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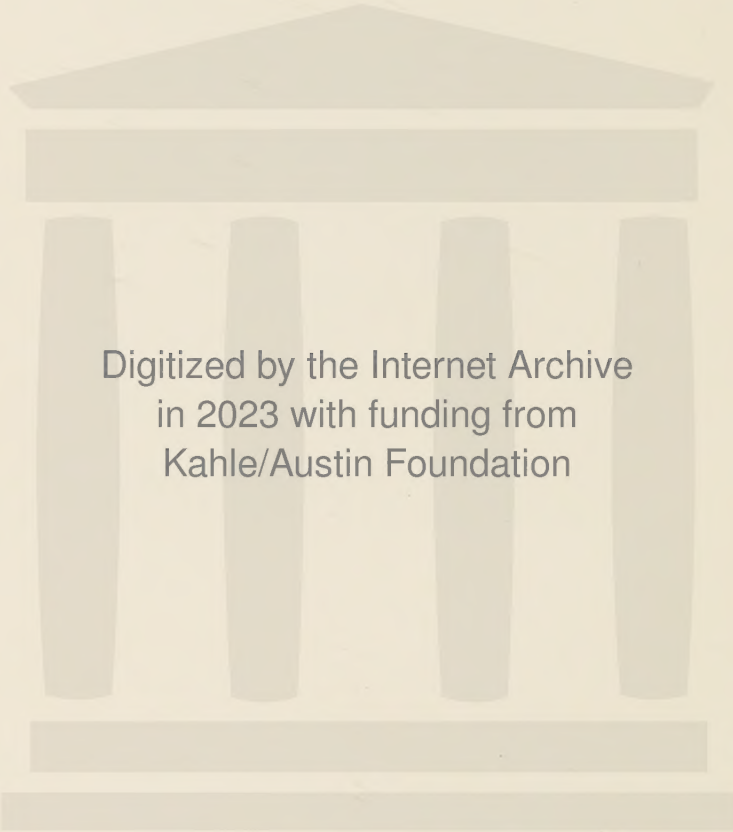
MAY 1974

INFECTIOUS DISEASES

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# THE MEDICAL CLINICS OF NORTH AMERICA

VOLUME 58 / NUMBER 3  
MAY 1974

*SYMPOSIUM ON*  
INFECTIOUS DISEASES

Phillip I. Lerner, M.D.,  
Martin C. McHenry, M.D., and  
Emanuel Wolinsky, M.D., *Guest Editors*

W. B. SAUNDERS COMPANY — Philadelphia · London · Toronto

W. B. Saunders Company: West Washington Square  
Philadelphia, Pa. 19105

12 Dyott Street  
London, WC1A 1DB

833 Oxford Street  
Toronto, Ontario M8Z 5T9

The Medical Clinics are also published in other languages,  
by the following:

Spanish Nueva Editorial Interamericana, S. A. de C. V., Cedro 512,  
Apartado 26370, Mexico 4, D.F., Mexico

Italian Piccin Editore, Via Porciglia, 10,  
35100 Padua, Italy

**THE MEDICAL CLINICS OF NORTH AMERICA**  
**May 1974                      Volume 58—Number 3**

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The Medical Clinics of North America is published every other month by W. B. Saunders Company, West Washington Square, Philadelphia, Pennsylvania 19105, at Hampton Road, Cherry Hill, New Jersey 08034. Subscription price is \$21.00 per year. Second class postage paid at Cherry Hill, New Jersey 08034. This issue is Volume 58, Number 3.

The editor of this publication is Albert E. Meier, W. B. Saunders Company, West Washington Square, Philadelphia, Pennsylvania 19105.

Library of Congress catalog card number 17-28505

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March 1975

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HENRY E. ZELLMANN, M.D., and

RICHARD A. OBERFIELD, M.D., *Guest Editors*



JOHN HOLMES DINGLE, M.D.

## *Dedication*

This symposium was presented to honor Dr. John Holmes Dingle, Elisabeth Severance Prentiss Professor of Preventive Medicine at Case Western Reserve University. It is especially appropriate not only because John Dingle made major contributions to our knowledge of infections caused by both bacteria and viruses, but also because he was a mentor and teacher of many of the participants in this symposium.

John H. Dingle was born in North Dakota and attended Washington University in Seattle where he received three degrees, B.S., Ph.D., and M.S. He then attended John Hopkins University where he completed his doctorate degree in microbiology in 1933. Following 2 years at the Upjohn Company, he entered Harvard Medical School, graduating in 1939. Following an internship in pediatrics, he was appointed Francis Weld Peabody Fellow at the Thorndike Memorial Laboratory, Boston City Hospital. From 1942 to 1946 he was the director of the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board at Fort Bragg, North Carolina. Finally, in 1946 he became chairman of the Department of Preventive Medicine at Case Western Reserve University.

John Dingle published over 300 scientific articles, of which 20 appeared before his graduation from Harvard. These early papers were concerned with such diverse subjects as the bacteriology of crab meat and the flavor of frozen peas. Most important were his observations on eastern equine encephalomyelitis and on *Hemophilus influenzae*, including the isolation of type b polysaccharide. As a medical student he also studied paroxysmal nocturnal hemoglobinuria with Hale Ham and 12 years later again published several papers on the mechanism of destruction of red cells in this disease.

After internship he joined the staff at the Thorndike Laboratory and published an extensive work on infectious diseases of mice. A large outbreak of meningococcal meningitis in Nova Scotia led Dingle, Thomas, and Finland to several investigations resulting in important observations on the bacteriologic, immunologic, epidemiologic, and preventive aspects of this disease. These publications remained the authoritative references for two decades.

In the summer of 1941, a high incidence of pneumonia was noted at Camp Claiborne, Louisiana. Late in December a team of investigators under Dr. Dingle studied the outbreak which was proven to be primary atypical pneumonia. This study led to the establishment of the Commission on Acute Respiratory Diseases at Fort Bragg and to John Dingle's lifelong interest in atypical pneumonia and all forms of respiratory disease. The war years were exciting, for respiratory infections were rampant. More important, John Dingle's leadership qualities were contagious, so that influenza, atypical pneumonia, Q fever, streptococcal infections, nonstreptococcal exudative tonsillitis, and acute respiratory disease became major targets for study. It would take several pages to summarize the major contributions of this group effort; suffice it to say that the epidemiology and etiology of these diseases were clarified, and the serum samples that were saved helped to establish the precise agents causing mycoplasma pneumonia and adenovirus disease of recruits.

The next phase in John Dingle's life began in 1946, when he brought a team to Cleveland to establish the Department of Preventive Medicine at Case Western Reserve University. Here the focus was primarily on the family as the epidemiologic unit. In 1964, Dingle, Badger, and Jordan published in monograph form a summary of a study of 25,000 respiratory illnesses observed in these families. In addition to this major effort, numerous other investigations of infections were instituted in his department.

Along with these clinical, epidemiologic, and laboratory investigations, Dr. Dingle carried a heavy load in the medical school. At the national level he was a member and president of the Armed Forces Epidemiological Board and served on numerous committees of the National Institutes of Health and was president of several national societies. His scholarly work and leadership qualities have been recognized by the Legion of Merit, Lasker Award, James D. Bruce Memorial Award, and Bristol Award for Distinguished Achievement in Infectious Diseases, and by election to the National Academy of Sciences.

It is sad to record that John Holmes Dingle died September 15, 1973 after a brief period of hospitalization. He gave medical science much, including not only new knowledge, but also those friendly and scholarly attributes that inspire and endure for years.

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## *Symposium on Infectious Diseases*

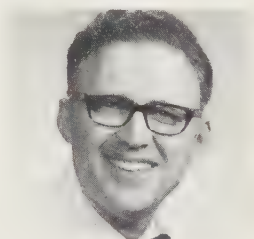


PHILLIP I. LERNER



MARTIN C. MCHENRY

## *Foreword*



EMANUEL WOLINSKY

In recent years, significant advances have been made in the understanding of infectious diseases and many potent new antimicrobial drugs have become available for clinical use. The clinical spectrum of serious infections has changed considerably—micro-organisms which rarely caused infection in the past have become significant causes of morbidity and mortality, especially in hospitalized patients with impaired resistance to microbial invasion. New clinical syndromes and pathogenic mechanisms of infection have been described. Emergence of resistance of pathogens to currently available antimicrobial drugs continues to be a serious problem. Knowledge of the bioavailability, potential toxicity, clinical efficacy and limitations of antimicrobial drugs has been accumulating at a rapid pace. Advances have also been made in understanding of fungal and viral infections and immunization procedures. Keeping abreast of the significant developments in the field of infectious diseases and antimicrobial chemotherapy is a matter of increasing difficulty. In organizing this symposium, we have selected topics which we hoped would be of timely interest to the practicing physician. The order of presentation of the topics was determined by the guest editors in an attempt to span the wide range of topics in a somewhat cohesive fashion.

The material presented in this volume represents the proceedings of the Cleveland Symposium on Infectious Diseases which was presented in Cleveland, Ohio, on June 13 and 14, 1973. The Symposium was dedicated to John H. Dingle, M.D., and was cosponsored by the Cleveland

Clinic Foundation and the American Society for Clinical Pharmacology and Therapeutics. With the exception of the invited guest participants, John G. Wagner, Ph.D., and Jan Schwarz, M.D., all the contributors to this volume were from Cleveland. This was possible largely because of the high degree of camaraderie of the physicians interested in infectious diseases in this city and their dedication to John H. Dingle, M.D.

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## Untoward Effects of Antimicrobial Agents on Major Organ Systems

*Ray A. VanOmmen, M.D.\**

The problem of adverse reactions to antibiotics should concern all physicians. Life-threatening and morbidity-causing factors of antibiotic therapy are mainly direct toxic or allergic reactions. Idiosyncratic reactions and individual intolerance to antimicrobial agents may be serious, and awareness of these phenomena may often prove life-saving. The possibility of adverse effects of antimicrobial agents must be considered at the time of initiating administration. Physicians must now be concerned not only with the infections they are treating but also with the diseases that may be caused by treatment.

It is not within the scope of this paper to consider all the adverse reactions to antibiotic therapy. Rather than the usual approach, whereby the antimicrobial agents are itemized with their numerous individual toxic effects, specific major organ systems were selected, and the significant untoward reactions related to their use are discussed.

### NEUROTOXICITY

#### Ototoxicity

The ototoxic reactions are among the most common and serious side effects of antibiotic usage, with potential for severe deafness and severe vestibular impairment. Fortunately, many of these effects can be avoided by careful selection of antibiotic dosage and attention to early symptoms of inner ear dysfunction. Although previous reports suggested that the site of toxicity may be the end organ, the cochlear nerve, or the central nuclei, recent evidence suggests that the loss is overwhelmingly concentrated at the hair cell level of the cochlea or vestibular apparatus, with the infrequently observed central lesions being secondary to trans-synaptic degeneration.

Clinically the toxicity may appear gradually with minor tinnitus and high-frequency hearing loss, but if these symptoms are neglected, rapid and severe deafness may result. Since some of the ototoxic antibiotics

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The neuromuscular blockade produced by kanamycin differs in that it is similar to that produced by succinylcholine, and therefore neostigmine may worsen the blockade. Polymyxin B and colistin also produce a noncompetitive blockade which is neostigmine-resistant. Polymyxin B<sup>29</sup> and colistin<sup>38</sup> cause respiratory arrest after as little as a single dose, or after prolonged treatment. It is often preceded by dyspnea, restlessness, and other central nervous system symptoms. Intravenous injections of calcium have been reported to be effective in the treatment of respiratory paralysis associated with these two antibiotics, but the primary treatment is controlled ventilation until the effect subsides. As predicted, we are now seeing reports of neuromuscular blockade associated with gentamicin therapy.<sup>60</sup>

All the antibiotics capable of causing neuromuscular blockade should be avoided in anesthetized patients, and care should be used in the concomitant administration of sedatives and narcotics; they are contraindicated for patients with myasthenia gravis.

### Miscellaneous Neurotoxic Reactions

Tetracycline may cause increased intracranial pressure as manifested by bulging of the fontanel in infants.<sup>14</sup> This benign but alarming reaction disappears promptly on cessation of therapy with the drug. Knowledge of the possible complications of tetracycline therapy is important since the differential diagnosis of this condition often involves life-threatening diseases.

Cerebral toxicity may be associated with massive intravenous injections of penicillin.<sup>47</sup> It is well known that penicillin is epileptogenic when injected directly into the central nervous system, and this has restricted its subarachnoid and intraventricular administration. Penicillin given intravenously in doses in excess of 25 million units daily, particularly in the elderly and in persons with renal impairment, may produce a syndrome of decreased consciousness, myoclonic jerking, and grand mal seizures.<sup>1, 50</sup> When penicillin therapy is discontinued or the dosage is reduced, improvement usually occurs within several hours.

Amphotericin B has been reported to cause a neurotoxic syndrome of tremor, incontinence, mental clouding, flaccid paralysis of arms and legs, and weakness of respiratory muscles.<sup>20</sup>

Of the other antibiotics, cycloserine in doses of greater than 1 gm. a day is particularly likely to cause myoclonic jerking and other seizures.<sup>17</sup>

## HEMATOTOXICITY

Among the blood dyscrasias that may be associated with the use of antibiotics are aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia, and hemolytic anemia. The most serious of these are aplastic anemia and agranulocytosis because of their frequency of occurrence and their high mortality.

### Aplastic Anemia

Chloramphenicol is now the leading single cause of drug-induced aplastic anemia in man. A distinction, however, should be made between

the reversible hematopoietic depression that frequently accompanies chloramphenicol therapy and the aplastic anemia that results from the administration of this drug.<sup>63</sup> Reversible toxicity from chloramphenicol is a pharmacologic action of the drug which can be induced in most if not all patients receiving large doses of the antibiotic.

This marrow depressive action is associated with an increase in serum iron, decrease in reticulocytes, and vacuolization of bone marrow cells. The biochemical mechanism of this effect is not well understood, but evidence suggests that bone marrow suppression results from inhibition of mitochondrial protein synthesis and consequent mitochondrial injury. Depression of the bone marrow may be more prevalent in patients receiving chloramphenicol who have hepatic and renal insufficiency.<sup>64</sup>

Even less understood is the mechanism by which chloramphenicol causes bone marrow aplasia. This type of toxicity usually has a late onset, even after completion of therapy, and is not necessarily related to dosage. It is characterized by an aplastic bone marrow, pancytopenia, and often a fatal outcome. Some investigators have reported that early detection of leukopenia or granulocytopenia and prompt discontinuance of chloramphenicol therapy may be followed by total recovery from hematopoiesis in 1 to 3 weeks. However, serial determinations of the white blood cell counts may not always be reliable in preventing disaster; in some patients the hematologic abnormalities do not develop until after therapy has been completed. The small risk of aplastic anemia should not contraindicate the use of chloramphenicol in life-threatening infections when there is no suitable alternative drug. However, one must be circumspect about the use of this agent, and repeated courses of therapy should be avoided whenever possible.

### **Agranulocytosis and Leukopenia**

The sulfonamides cause agranulocytosis by an immune phenomenon, with a direct myelotoxic effect evident in the arrest of bone marrow maturation at the myeloblast stage. The granulocytopenia is not related to dosage or blood content of the drug, and the reaction may appear suddenly or after a period of progressive neutropenia. Fortunately, most patients recover spontaneously with supportive care, but the return of granulocytes to normal levels may be considerably delayed after administration of the drug is discontinued.

Chloramphenicol may at times cause this selective bone marrow depressive reaction without affecting the other marrow elements. Protracted or irreversible granulocytopenia of the chronic type is best exemplified by that caused by chloramphenicol, and even transition to leukemia has been reported.<sup>15</sup>

Bone marrow depression with significant neutropenia has been reported secondary to administration of methicillin.<sup>28,33</sup> This toxic effect was reversible in all patients after cessation of therapy. Other penicillins which have been implicated as agents which may cause leukopenia are ampicillin<sup>18</sup> and more recently carbenicillin.<sup>41</sup>

There have been reports also of neutropenia associated with cephalothin<sup>8</sup> and cephapirin<sup>25</sup> therapy.

## Thrombocytopenia

The sulfonamides and chloramphenicol have been noted to cause thrombocytopenia, which is an infrequent and usually a minor adverse hematologic drug reaction. The exact mechanism is not always understood, but in many instances is caused by an immune reaction. The presenting signs are usually petechiae, easy bruising, or bleeding. Bleeding from drug-related thrombocytopenia seldom is severe, and recovery is usually rapid after use of the drug has been discontinued.

## Hemolytic Anemia

Sulfonamides and nitrofurantoin derivatives are antibacterial agents which cause hemolytic anemia. These agents are among a long list of hemolytic oxidant drugs that activate this process in patients whose erythrocytes are deficient in the enzyme glucose-6-phosphate dehydrogenase. Patients with this genetic deficiency in the erythrocytes are unable to generate triphosphopyridine nucleotide in its reduced form, and as a result are unable to produce reduced glutathione, and these metabolites are necessary to reverse the oxidation of hemoglobin. The erythrocytes are unable to tolerate the concentration of the drugs produced by ordinary therapeutic doses. Hemoglobin is oxidized and, by mechanisms not entirely understood, the erythrocyte is hemolyzed.<sup>23</sup>

Hemolysis by these drugs is not entirely limited to patients with this enzyme deficiency, although these susceptible persons should be tested before administration of these drugs. It can occasionally occur in other patients when the concentration of the drug is sufficiently high.<sup>10</sup> High concentrations of the drug in the blood may be related to excessive dosage or to delayed excretion due to renal insufficiency. In addition to causing hemolysis, nitrofurantoin may occasionally cause an associated megaloblastic erythropoiesis.<sup>40</sup>

Immunohemolytic anemia induced by the administration of large doses of penicillin has been reported.<sup>9, 56</sup> This anemia is accompanied by reticulocytosis, hyperbilirubinemia, a decrease in the life span of erythrocytes, and a strongly positive direct Coombs' test. The serum of these patients has a circulating antipenicillin antibody that is capable of mediating a hemolytic anemia.

Cephalothin may give rise to a positive reaction to a direct Coombs' test.<sup>36</sup> The primary mechanism of the positive Coombs' reaction has been shown to be the result of nonspecific (nonimmune) binding of a protein complex to the red blood cell surface and is usually not associated with hemolytic anemia. It may, however, interfere with the cross-matching of blood if the minor match is performed.

## Miscellaneous Hematotoxic Reactions

In most patients receiving amphotericin B therapy a severe anemia develops. The anemia appears to be related to therapy and not to the underlying fungal infection, since it develops despite clinical improvement and remits when use of the drug is stopped. Anemia also precedes the azotemia that may occur during treatment. It has been postulated that this anemia is a consequent of defective reutilization of iron.<sup>44</sup>

The tetracyclines have been shown to be able to interfere with blood

coagulation, particularly in patients who have intrinsic tendencies to bleed. These agents apparently alter the physicochemical characteristics of the blood lipoproteins and thereby affect lipid factors essential for the normal blood-clotting process.<sup>48</sup> Antimicrobial agents that have been associated with a slight increase in the prothrombin time include the penicillins, novobiocin, and the sulfonamides.

Carbenicillin therapy has been reported to be suspect in hemorrhagic phenomenon associated with coagulopathy, particularly in azotemic patients.<sup>58</sup>

## HEPATOTOXICITY

Numerous agents including several antibiotics used in the treatment of infectious diseases may produce hepatic dysfunction with or without jaundice. It has been observed that the tetracyclines may injure the liver, and clinical evidence of hepatic dysfunction developed in patients receiving large doses orally or intravenously. Microscopic study of the liver revealed fine vacuoles, cytoplasmic changes, and an increase in fat.<sup>27</sup> Most reactions of this type develop in patients receiving 2 gm. or more of the drug per day parenterally; however, this effect may also occur when large quantities are administered orally or with a combination of the two modes of administration.

Six obstetric patients treated with large intravenous injections of tetracycline died after nausea, vomiting, fever, jaundice, acidosis, azotemia, and terminal hypotension developed.<sup>47</sup> Necropsy revealed fine-droplet fatty metamorphosis of all portions of the lobule, but no evidence of inflammation or biliary obstruction.

Azotemia may considerably increase the content of the tetracyclines in serum, and therefore great care must be taken in their administration to patients with renal insufficiency, to protect against the possibility of hepatotoxicity. Patients with pre-existing hepatic disease who received tetracycline were found on biopsy to have an increase in fat in the liver.<sup>45</sup> The chances of hepatotoxicity from tetracycline administration appear to be related to daily dosage, duration of therapy, pregnancy, underlying hepatic disease, concurrent use of other hepatotoxic drugs, and impaired renal function.

Erythromycin estolate, which is the lauryl sulfate salt of erythromycin propionate, may produce hepatic dysfunction after 1 or 2 weeks of continuous therapy or after several courses of the drug.<sup>12</sup> The absence of reports of jaundice with other forms of erythromycin suggests that the hepatotoxicity is specific for this ester. Jaundice, abnormal liver function tests, and eosinophilia may occur, but usually subside rapidly when use of the drug is discontinued. The effect seems to be one of intrahepatic cholestasis resulting from a form of sensitization. That hypersensitivity is responsible for this syndrome is suggested by its rarity, by the fact that it usually does not appear with first exposure to the drug unless it is continued for 10 or more days, and because it is not related to dosage.

Triacetyloleandomycin has been found to impair hepatic function in many patients receiving this drug for 2 weeks or longer, although jaun-

dice develops infrequently.<sup>51</sup> The dosage of medication in these patients was not above the amount usually recommended. The abnormalities were demonstrated by impaired sulfobromophthalein excretion, abnormal cephalin flocculation test, and elevated serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) concentrations. In patients without jaundice, these liver function tests rapidly return to normal within a week after withdrawal of the drug, although the cephalin flocculation test may remain abnormal in some patients for a few additional weeks. Laboratory tests and biopsy studies indicate that the type of hepatic abnormality and the jaundice have hepatocellular as well as cholestatic features.

Novobiocin may cause a yellow discoloration of the skin, sclera, and serum in a small percentage of patients; this effect is ascribed to the presence of a yellow pigment produced by the metabolism of novobiocin.<sup>62</sup> In infants, however, there appears to be some possibility of neonatal hyperbilirubinemia during administration of novobiocin, suggestive of interference of the drug with bilirubin metabolism.<sup>53</sup>

Sulfonamides and amphotericin B may occasionally cause hepatic injury and failure, and the available data suggest that the hepatic lesion is characterized by hepatocellular damage with toxic degeneration.<sup>11, 12</sup> Isoniazid is another agent capable of causing hepatotoxicity.

Elevation of the SGPT concentration has been reported with the use of a considerable number of antibiotics, including ampicillin, oxacillin, cloxacillin, lincomycin, colistin, cephalothin, and nalidixic acid, but the exact significance is not clear.

## NEPHROTOXICITY

A large number of antibiotics currently in clinical use have a potentially nephrotoxic effect. These antimicrobial agents are of great value in treating patients with serious sepsis. It is fortunate that the nephrotoxicity of these drugs appears to be largely reversible, if their administration is discontinued soon enough. It is essential that when these agents are administered renal function is regularly monitored. Patients having pre-existing renal disease appear to be particularly sensitive to many of these agents, but even uremic patients should not be denied the life-saving effects of these drugs when they are indicated; they can be given under these circumstances providing the principles of a modified dosage schedule are closely followed. The concomitant use of renal toxic agents should be avoided or should be undertaken with great caution.

Kanamycin and neomycin are closely related, both chemically and in antimicrobial action. Since neomycin has a higher degree of toxicity in general, kanamycin has virtually replaced neomycin for parenteral use. The renal lesion produced by these antibiotics primarily involves the proximal convoluted tubules, and clinically is evidenced by a decrease in glomerular filtration rate, in para-aminohippuric acid clearance, and in maximal tubular concentration.

Polymyxin B and colistin, antibiotics that are closely related chemically, may be considered together. Both are potentially nephrotoxic, and

the main differences are in structure and dosage. These drugs also produce proximal tubular necrosis, although they are fairly well tolerated in patients without pre-existing renal impairment. In azotemic patients receiving these drugs an alarming increase in serum creatinine and blood urea nitrogen may develop, with only a slow return to normal values after therapy has been discontinued or reduced.<sup>13, 22</sup>

Gentamicin was observed to cause renal tubular necrosis in dogs during studies of acute toxicity.<sup>61</sup> Adverse renal reactions have also been observed in a small percentage of patients receiving this antibiotic.<sup>4</sup> Renal function should be monitored when administering this antibiotic, and considerable caution should be exercised in its use when there is pre-existing renal impairment.<sup>31</sup> There is a possibility that administration of the combination of gentamicin and cephalothin may potentiate renal toxicity.<sup>2</sup>

Cephaloridine is capable of producing adverse effects on the kidneys; however, such effects are infrequent when the recommended dosage of 4 gm. or less daily is administered to patients without pre-existing renal impairment.<sup>51</sup> Renal function should be followed during therapy and use of the drug discontinued should impairment develop. Cephaloridine should not be used in patients with potentially treatable renal disease. In anephric patients cephaloridine may be given in reduced dosage because it has no serious extrarenal side effects.

Bacitracin has notable nephrotoxic properties destructive of both the proximal and distal convoluted tubules. Formerly it was frequently used parenterally in the treatment of penicillin-resistant staphylococcal infections; however, with the current availability of more effective and less toxic agents, the therapeutic role of bacitracin for parenteral therapy has been largely supplanted.

Amphotericin B is the only available drug effective in preventing death from a number of serious systemic fungal infections and therefore continues to be widely used despite numerous toxic properties. The accepted nephrotoxicity of amphotericin B is underlined by the fact that the daily dosage of the drug is usually governed by the degree of azotemia present rather than by the therapeutic response of the patient. The clinician's decision to use this drug must be made with the full understanding that impaired renal function and damaged renal structure occur in most patients. Amphotericin B produces renal vasoconstriction with reduction in renal blood flow, which may be an important factor in the glomerular and tubular damage and calcium deposition noted in patients after they have received this agent.<sup>5</sup> Renal tubular acidosis has been reported as a complication of therapy with amphotericin B. Renal function may improve after cessation of therapy, but often there are various degrees of permanent residual damage.

The ingestion of deteriorated, outdated tetracycline has been observed to cause a syndrome of nausea, vomiting, proteinuria, acidosis, glycosuria, and aminoaciduria.<sup>16, 19</sup> Renal biopsy in such cases<sup>32</sup> reveals severe tubular changes. The glomeruli are also affected, and this explains the massive proteinuria. This pathologic process resembling the Fanconi syndrome appears to be entirely reversible in from 4 to 6 weeks after withdrawal of use of the antibiotic. The possibility of this potentially

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serious renal toxic effect dictates that the physician not prescribe tetracycline in an amount to exceed that needed for a single illness, and that the patient be instructed to discard leftover medication.

Nephropathy associated with penicillin and its homologues, particularly methicillin, has been reported in recent years.<sup>3, 46</sup> The basis for this adverse change is believed to be a hypersensitivity reaction causing diffuse interstitial nephritis. The syndrome is often initiated by spiking fever, malaise, anorexia, and abdominal aching, and may be associated with eosinophilia and skin rash. The renal manifestations most frequently include hematuria, pyuria, albuminuria, and oliguria. Fortunately, the patients recover fairly rapidly when this complication is recognized and therapy is discontinued.

Certain sulfonamides may cause severe renal damage by deposition of crystalline aggregates, leading to development of irritation and obstruction. Two other mechanisms, toxic nephrosis and hypersensitivity reaction, rarely are factors in the production of tubular necrosis or necrotizing angitis of the kidneys.

## MISCELLANEOUS ORGAN TOXICITY

### Cardiovascular Complications

The parenteral administration of lincomycin has been reported to cause instances of hypotension. This is usually related to rapid intravenous administration, and a few episodes of cardiopulmonary arrest have been reported after rapid or so-called bolus administration.<sup>37</sup> There have not been any serious reactions noted with clindamycin, although some episodes of tachycardia and minor arrhythmias have been observed with rapid intravenous administration.

### Pulmonary Complications

The lungs are particularly susceptible to superinfections following the administration of antibiotics, although the presence of abnormal bacteria in the sputum must be critically evaluated to distinguish simple colonization from infection. The lungs may also be involved in drug-induced syndromes such as lupus erythematosus and vasculitis.

Of increasing interest in recent years has been the pulmonary disorder described as pulmonary eosinophilia. The drug most commonly causing this syndrome at present is probably nitrofurantoin.<sup>21</sup> Characteristically the illness is abrupt in onset, with shaking chills, high fever, dyspnea, and cough that is productive of mucoid sputum. The patient is visibly in respiratory distress with tachypnea, and rales are generally heard in both bases, but wheezing is notably absent. Peripheral eosinophilia is present in varying degrees. Roentgenograms typically show infiltration, especially in the lung bases, with consolidation or effusion. This syndrome has been confused with pulmonary embolism, congestive heart failure, and other cardiopulmonary diseases, but may be differentiated by electrocardiography and other methods and signs. Specific treatment probably is unnecessary in most cases since recovery usually is rapid once the nitrofurantoin is withdrawn, but antihistamines and corticosteroids have been effective for symptomatic relief.

## Dermatologic Complications

Dermatitis may complicate the administration of many of our antibiotic agents but fortunately the more serious types, such as toxic epidermal necrolysis and generalized exfoliative dermatitis, are not seen too frequently. Fixed drug eruptions and photosensitive drug eruptions are of considerable interest.

Eruptions due to ampicillin merit special mention because of their high incidence and some very unusual characteristics of their course.<sup>10</sup> There is evidence that the higher the dose of ampicillin the higher the incidence of eruptions associated with its use. In patients receiving 8 gm. or more daily the incidence may reach 20 per cent, whereas in a large series of patients receiving smaller doses orally, the eruption rate is 3 to 8 per cent. The one intriguing exception to this pattern has been the extremely high incidence of eruptions, which approaches 100 per cent in patients who have infectious mononucleosis and are receiving this drug regardless of the dosage used. In contrast, patients with infectious mononucleosis receiving other penicillins have shown no increase in incidence of skin eruptions. The explanation for this peculiar response is still not known.

## Gastrointestinal Complications

Although the gastrointestinal tract bears most of the brunt of the complications of antibiotic treatment, most reactions are not serious. Stomatitis and glossitis occur frequently, especially with the use of broad spectrum antibiotics, and one often finds that superinfection with *Candida albicans* is responsible. *Candida* esophagitis is not uncommon and this may be a difficult diagnostic problem. Cessation of antibiotic treatment is often all that is necessary in mild infections, but treatment with oral nystatin or even oral amphotericin B is effective in the management of an established infection.

There are very few antibiotics which cannot be included in a list of those that may on occasion cause anorexia, nausea, or vomiting. Clindamycin has been known to cause mild gastrointestinal symptoms, but there has been a report of 3 patients who had severe protracted colitis associated with treatment with the drug.<sup>6</sup>

An interesting complication associated with neomycin therapy is intestinal malabsorption and steatorrhea.<sup>13</sup> This is associated with large dosage and extended therapy. Changes which have been noted in the small intestine mucosa resemble those of nontropical sprue, but are much less severe and are readily reversible with cessation of therapy.

## SUMMARY AND CONCLUSION

The adverse reactions of antimicrobials on major organ systems has been reviewed to alert the physician again to the significant and often life-threatening effects of these widely used and effective therapeutic agents. Potentially harmful effects of the use of antibiotics must never discourage a physician from their administration for any condition in which they are clearly indicated, because the use of any potent therapeutic

tic agent is accompanied by a calculated risk. To be concerned only with their potential danger is no less unrealistic and unwise than to accept them as invariably applicable, completely beneficial, and entirely harmless.

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## Relevant Pharmacokinetics of Antimicrobial Drugs

*John G. Wagner, Ph.D.\**

### GOALS OF ANTIMICROBIAL THERAPY

The basic goal of antimicrobial therapy is to achieve steady state blood and tissue levels of the antimicrobial agent that are both efficacious and nontoxic. Steady state levels are characterized by the concentration/time profile reproducing itself between any given two doses. When a given dose of a drug is administered at uniform time intervals, the blood concentration/time profile will change in such a manner that the peak concentrations increase with increases in the number of doses until eventually a steady state is reached. This pattern has been termed drug accumulation, and is readily visualized graphically in Figure 2 of this paper. Ideally one would have as a goal that the steady state concentration/time profile is such that the nadir in the curve is always above some required concentration, such as the minimum inhibitory concentration (MIC) and the peak is always below the level which gives side effects or toxicity. However, with antimicrobial therapy it is still unclear whether it is the integrated concentration time (or area under the curve) which is most important or the peak concentration. The problem is complicated since frequently the peak and the area under the curve are closely correlated.

Drug accumulation can be a serious problem when the ratio of the half-life of elimination of the drug to the dosage interval (time between doses) is large. If a drug such as phenobarbital, with a half-life of 2 to 6 days in man, is administered every 8 hours the plasma concentrations of the drug will continue to build up for long periods of time. If the dose is high enough, dangerous levels may be reached. Drug accumulation occurs because the rate of intake in a given dosage interval exceeds the

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This paper was originally presented under the title, "Relevant Pharmacokinetics of Antimicrobial Drugs Including Uses in Renal Failure," at the Cleveland Symposium on Infectious Diseases, The Cleveland Clinic Educational Foundation, June 13 and 14, 1973.

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rate of loss in that same dosage interval. At the steady state the rates of intake and loss are equal in each dosage interval.

With antimicrobial therapy the patient is usually most ill when the antimicrobial agent is first administered. This is why the author believes that a loading dose should almost always be administered when antimicrobial therapy is initiated. However, to calculate the appropriate loading dose one has to know two things: (a) the steady-state blood levels one ultimately wishes to attain; and (b) the half-life of elimination of the antimicrobial agent, or blood levels observed after single doses of the agent. It is the purpose of this paper to show how blood levels of drugs after multiple doses can be predicted with pencil and paper from blood levels observed after single doses, and to present a simple method of making adjustments in dosage for patients with impaired renal function.

### PREDICTION OF BLOOD LEVELS OF DRUGS AFTER MULTIPLE DOSES

Kinetic linearity or linear pharmacokinetics may be defined as direct proportionality of transfer rates to concentrations or differences in concentrations.<sup>5</sup>

If a drug obeys linear pharmacokinetics,<sup>5,9-10,12</sup> then each dose of drug, in essence, acts independently of every other dose. Until there is evidence to the contrary, linear pharmacokinetics are usually assumed, particularly for drugs administered in therapeutic doses to human patients. Predictions of blood (plasma or serum) concentrations of a drug following multiple doses are usually made from the corresponding concentrations measured after a single dose of drug. Both simple<sup>14,15</sup> and complicated<sup>2,6,11,12</sup> equations which allow one to make such predictions have been published. The most complicated linear pharmacokinetic equation used to date to make such predictions is the four term exponential equation used by Wagner et al.<sup>13</sup> to predict multiple dose plasma concentrations of propoxyphene in man.

Scientists acquainted with pharmacokinetics have known for many years that such predictions can be made with pencil and paper, but Ballard<sup>1</sup> seems to be the only author who has published about this method. The method is appropriately called the superposition or overlying principle, but does not involve the use of an equation as elaborated by Westlake.<sup>14</sup> The method is illustrated in Table 1. The blood levels measured after a single dose of drug are the nonbracketed numbers shown in column 3 under "Dose 1" in Table 1. These were measured 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after the single dose of drug. The "blood levels" in Table 1 are actually theoretical blood levels generated by means of equation B shown in the Appendix. Such theoretical blood levels were used since the results achieved by the superposition principle could be compared with actual known values of corresponding "multiple dose blood levels" generated by means of equation E shown in the Appendix.

In the example shown in Table 1 it is assumed that one wishes to predict multiple dose blood levels from the single dose blood levels when

the same dose is administered every 6 hours. The single dose blood levels are plotted on cartesian coordinate graph paper in Figure 1A. It was also found that for this particular set of blood levels a semilogarithmic plot of the blood level *versus* time was apparently linear in the 6 to 12 hour range. This plot is shown in Figure 1B. In actual practice one could fit a line by sight through the points shown in Figure 1B, and then extrapolate to be able to predict concentrations out to 36 hours (time needed

**Table 1.** *Superposition or Overlaying Principle for Prediction of Blood Levels After Multiple Doses in a Linear System*

DOSE NUMBER	TIME (Hours)	DOSE 1	DOSE 2	DOSE 3	DOSE 4	DOSE 5	DOSE 6	TOTAL = $C_n(t)$
1	0	0						0
	0.5	38.84						35.84
	1	58.63						58.63
	2	69.86						69.86
	3	65.93						65.93
	4	57.94						57.94
2	5	49.57						49.57
	6	41.96	0					41.96
	6.5	(38.53)	38.84					77.37
	7	35.36	58.63					93.99
	8	29.74	69.86					99.60
	9	25.00	65.93					90.93
3	10	21.01	57.94					78.95
	11	17.65	49.57					67.22
	12	14.83	41.96	0				56.79
	12.5	(13.61)	38.53	38.84				90.98
	13	(12.48)	35.36	58.63				106.5
	14	(10.49)	29.74	69.86				110.1
4	15	(8.82)	25.00	65.93				99.75
	16	(7.41)	21.01	57.94				86.36
	17	(6.23)	17.65	49.57				73.45
	18	(5.24)	14.83	41.96	0			62.03
	18.5	(4.81)	13.61	38.53	38.84			95.79
	19	(4.41)	12.48	35.36	58.63			110.9
5	20	(3.70)	10.49	29.74	69.86			113.8
	21	(3.11)	8.82	25.00	65.93			102.9
	22	(2.62)	7.41	21.01	57.94			88.98
	23	(2.20)	6.23	17.65	49.57			75.65
	24	(1.85)	5.24	14.83	41.96	0		63.88
	24.5	(1.70)	4.81	13.61	38.53	38.84		97.49
6	25	(1.56)	4.41	12.48	35.36	58.63		112.4
	26	(1.31)	3.70	10.49	29.74	69.86		115.1
	27	(1.10)	3.11	8.82	25.00	65.93		104.0
	28	(0.92)	2.62	7.41	21.01	57.94		89.90
	29	(0.78)	2.20	6.23	17.65	49.57		76.43
	30	(0.65)	1.85	5.24	14.83	41.96	0	64.53
	30.5	(0.60)	1.70	4.81	13.61	38.53	38.84	98.09
	31	(0.55)	1.56	4.41	12.48	35.36	58.63	113.0
	32	(0.46)	1.31	3.70	10.49	29.74	69.86	115.6
	33	(0.39)	1.10	3.11	8.82	25.00	65.93	104.4
	34	(0.33)	0.92	2.62	7.41	21.01	57.94	90.23
	35	(0.27)	0.78	2.20	6.23	17.65	49.57	76.70
	36	(0.23)	0.65	1.85	5.24	14.83	41.96	64.76

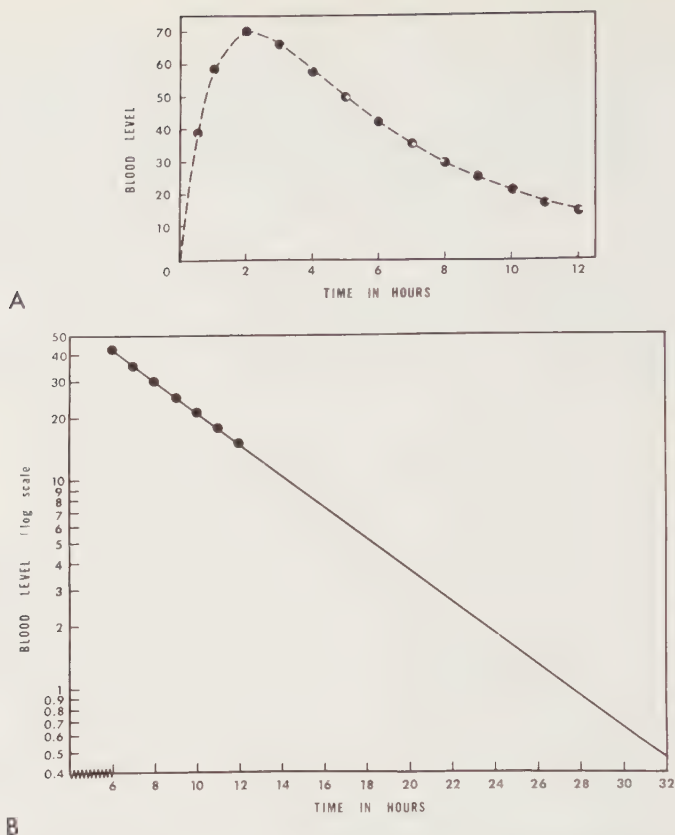


Figure 1. A, Rectilinear plot of single dose blood levels shown as non-bracketed numbers in third column of Table 1. B, Semilogarithmic plot of single dose blood levels in 6 to 12 hour range, with line extrapolated to be able to predict blood levels at later times.

for 6 doses) which was used in the example. The author was a little fancier and fitted the least squares line through the points. This is discussed in the Appendix (equations C and D).

To apply the superposition method, one simply copies down the blood levels in separate columns headed Dose 2, Dose 3, etc., staggering them such that one starts again at a time equal to the dosage interval (which is every 6 hours in the example). Note that one always has to put the value "zero" at zero time, one dosage interval, two dosage intervals (i.e. at 0, 6, 12, 18, 24, and 36 hours in the example). Once the table is complete for the number of doses desired, one simply adds up the "blood levels" by rows. These totals are shown under the last column, headed  $C_n(t)$  in Table 1. Thus  $C_n(t)$  represents the predicted multiple dose blood level after the  $n$ th dose at time  $t$ , measured from time of administration of the first dose.

The predicted multiple dose blood levels (column 9 of Table 1) are plotted against time  $t$  (column 2 of Table 1) in Figure 2. In this example it takes about four doses of drug to essentially attain the steady-state at

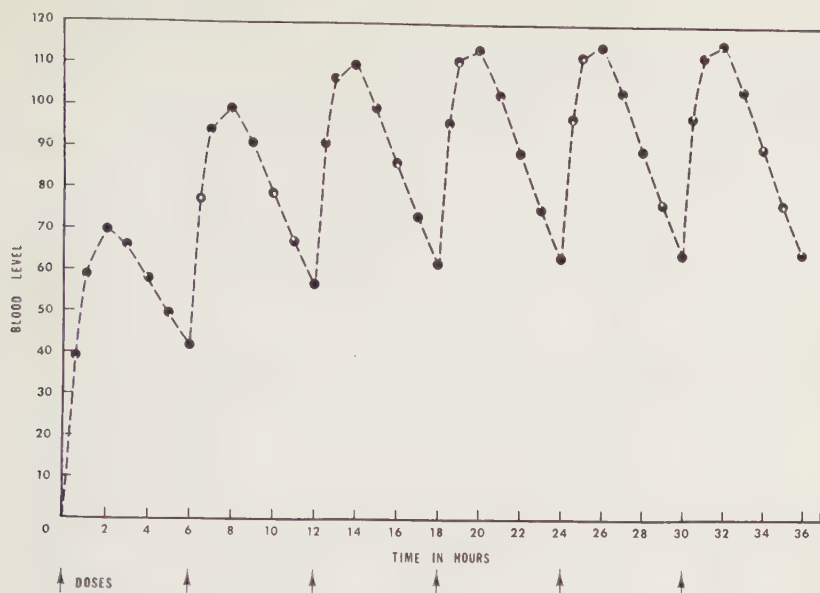


Figure 2. Plot of predicted multiple dose blood levels when no loading dose given (data from last column of Table 1).

which time the curve in each dosage interval essentially reproduces itself.

## SIMPLE ESTIMATION OF LOADING DOSE

One can administer a loading dose,  $D^*$ , as an initial dose, followed by maintenance doses,  $D$ , at uniform time intervals,  $\tau$ , such that the equilibrium (steady) state is essentially reached at once. The appropriate loading dose may be estimated reasonably accurately by means of equation 1.

$$D^* = D \left[ \frac{\text{Peak blood level at equilibrium state}}{\text{Peak blood level after first dose}} \right] \quad [1]$$

Assuming the blood levels after the sixth dose represent the equilibrium state values then we can substitute into equation 1 from the data in Table 1 to obtain equation 2.

$$D^* = \frac{115.6}{69.86} D = 1.65D \quad [2]$$

(Using the more exact equation H in the Appendix a value of 1.61 instead of 1.65 was obtained). To test the results with the data shown in Table 1, each blood level in column 3 of Table 1 was multiplied by 1.65, and the resulting values are shown in column 3 under Dose 1 of Table 2.

Table 2. Predicted Blood Levels with Loading Dose

DOSE NUMBER	TIME (Hours)	DOSE 1	DOSE 2	DOSE 3	DOSE 4	DOSE 5	DOSE 6	TOTAL = $C_n(t)$
1	0	0						0
	0.5	64.09						64.09
	1	96.74						96.74
	2	115.3						115.3
	3	108.8						108.8
	4	95.60						95.60
2	5	81.79						81.79
	6	69.23	0					69.23
	6.5	63.57	38.84					102.4
	7	58.34	58.63					117.0
	8	49.07	69.86					118.9
	9	41.25	65.93					107.2
3	10	34.67	57.94					92.61
	11	29.12	49.57					78.69
	12	24.47	41.96	0				66.43
	12.5	22.46	38.53	38.84				99.83
	13	20.59	35.36	58.63				114.6
	14	17.31	29.74	69.86				116.9
4	15	14.55	25.00	65.93				105.5
	16	12.23	21.01	57.94				91.18
	17	10.28	17.65	49.57				77.50
	18	8.65	14.83	41.96	0			65.44
	18.5	7.94	13.61	38.53	38.84			98.92
	19	7.28	12.48	35.36	58.63			113.8
5	20	6.11	10.49	29.74	69.86			116.2
	21	5.13	8.82	25.00	65.93			104.9
	22	4.32	7.41	21.01	57.94			90.68
	23	3.63	6.23	17.65	49.57			77.08
	24	3.05	5.24	14.83	41.96	0		65.08
	24.5	2.81	4.81	13.61	38.53	38.84		98.60
6	25	2.57	4.41	12.48	35.36	58.63		113.5
	26	2.16	3.70	10.49	29.74	69.86		115.9
	27	1.82	3.11	8.82	25.00	65.93		104.7
	28	1.52	2.62	7.41	21.01	57.94		90.50
	29	1.29	2.20	6.23	17.65	49.57		76.94
	30	1.07	1.85	5.24	14.83	41.96	0	65.94
	30.5	0.99	1.70	4.81	13.61	38.53	38.84	96.48
	31	0.91	1.56	4.41	12.48	35.36	58.63	113.4
	32	0.76	1.31	3.70	10.49	29.74	69.86	115.9
	33	0.64	1.10	3.11	8.82	25.00	65.93	104.6
	34	0.54	0.92	2.62	7.41	21.01	57.94	90.44
	35	0.45	0.78	2.20	6.23	17.65	49.57	76.88
	36	0.38	0.65	1.85	5.24	14.83	41.96	64.91

Hence these "blood levels" simulate the situation if a loading dose 1.65 times the maintenance dose had been administered initially. The rest of Table 2 is completed in the same manner as Table 1, since the maintenance doses are lower and all the same size. Again the rows are summed, giving the totals shown in column 9 of Table 2. The latter data are plotted in Figure 3, and show that the equilibrium state was reached essentially at once under the conditions above.

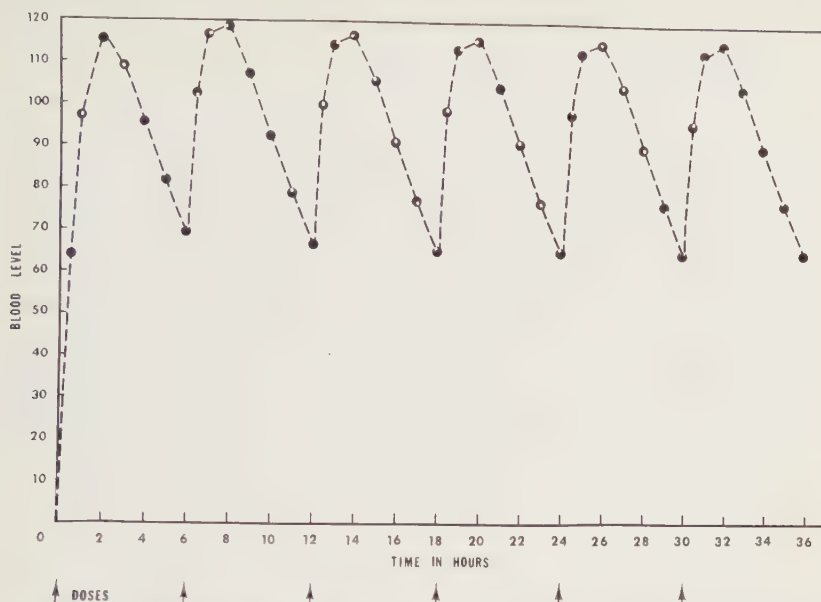


Figure 3. Plot of predicted multiple dose blood levels when loading dose is calculated by equation 4, and followed by same maintenance doses as in Figure 2 (data from last column of Table 3).

### PITFALLS OF THE SUPERPOSITION METHOD

The method illustrated is only valid when the pharmacokinetics are linear and elimination of the drug from the body obeys first order kinetics. For accurate predictions one also has to extrapolate the true terminal log-linear blood level data on semilogarithmic graph paper. The points chosen must be in the post-absorptive, post-tissue distribution phase. Hence blood level measurements must be made for a long enough period of time to establish the log-linear terminal phase *and* provide enough points in that phase to establish the line. A reasonable general rule is that the blood levels must be followed long enough that the last blood level measured is between one fifth and one twentieth of the peak blood level. The lower one can measure, the more assured one is that the appropriate data are being used to make the extrapolation.

An example showing where an error could be made is shown in Figure 4. Data plotted in Figure 4 were generated with equation J in the Appendix. Using the blood levels in the 12 through 28 hour range (solid line in Figure 4) a rate constant of  $0.1005 \text{ hours}^{-1}$  was obtained, which is very close to the true value of  $0.1000 \text{ hours}^{-1}$ . However, if one used the blood levels in the 2 through 8 hour range (dotted line in Figure 4) a rate constant of  $0.1411 \text{ hours}^{-1}$  is obtained. Extrapolation of the solid line would give correct values to apply the superposition or overlaying principle, whereas extrapolation of the dotted line would give incorrect values and a poor prediction of multiple dose blood levels.

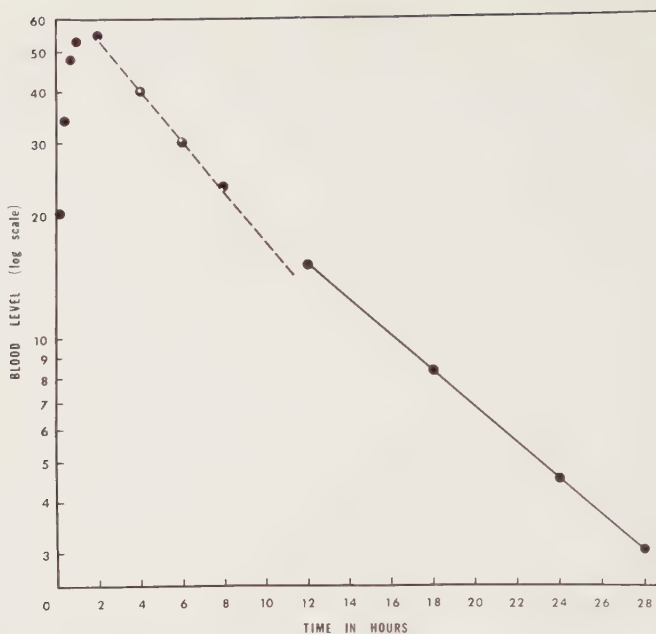


Figure 4. Data generated by equation H of the Appendix plotted on semilogarithmic graph paper. The solid line gives the correct elimination rate constant and half-life. The dotted line gives a meaningless rate constant and half-life.

It has become common practice by many not well acquainted with pharmacokinetics to perform the operations shown in Figure 4 and report two rate constants or their corresponding half-lives. This practice has no theoretical foundation and is extremely misleading. The rate constant or half-life estimated from the *terminal* log-linear line are the numbers which are meaningful, and those which must be used in any pharmacokinetic calculation.

If a drug obeys Michaelis-Menten elimination kinetics, then the superposition principle will provide an *underestimate* of the multiple dose blood levels.

### ADJUSTING DOSAGES IN PATIENTS WITH IMPAIRED RENAL FUNCTION

The literature up to and including 1970 was reviewed by Wagner,<sup>12</sup> who reported that Finland and co-workers published several papers in 1959 which showed the persistence of antibiotics in the blood of patients with renal failure. Ten years later Dettli<sup>3</sup> showed the mathematical relationships which may be expected to hold. These relationships were elaborated further and illustrated by Wagner.<sup>12</sup>

The appropriate relationship is that the overall rate constant for elimination of drug by the body,  $K_{el}$ , (expressed as per cent per hour

rather than the usual fraction per hour) is linearly related to the endogenous creatinine clearance as shown in equation 3.

$$K_{\%} = a + b \cdot Cl_{cr} \quad [3]$$

where  $a$  is a constant and represents that portion of the elimination rate constant which is due to nonrenal losses of drug (it is the intercept of a plot of  $K_{\%}$  versus  $Cl_{cr}$ ), and  $b \cdot Cl_{cr}$  represents the portion of the elimination rate constant which is due to renal losses of the drug. Thus,  $b$  is the slope of the plot of  $K_{\%}$  versus  $Cl_{cr}$ , where  $Cl_{cr}$  is the endogenous creatinine clearance. An example is shown in Figure 5 in which the data of McHenry et al.<sup>7</sup> for gentamicin are plotted in conformity with equation 3. When  $Cl_{cr}$  is expressed in ml. per min. per 1.73 m<sup>2</sup> body surface area, the least squares regression line shown in the figure has an intercept,  $a$ , equal to 0.23, and a slope,  $b$ , equal to 0.249. To calculate the elimination half-life for any given value of  $K_{\%}$  one uses equation 4.

$$t_{1/2} = 69.3/K_{\%} \quad [4]$$

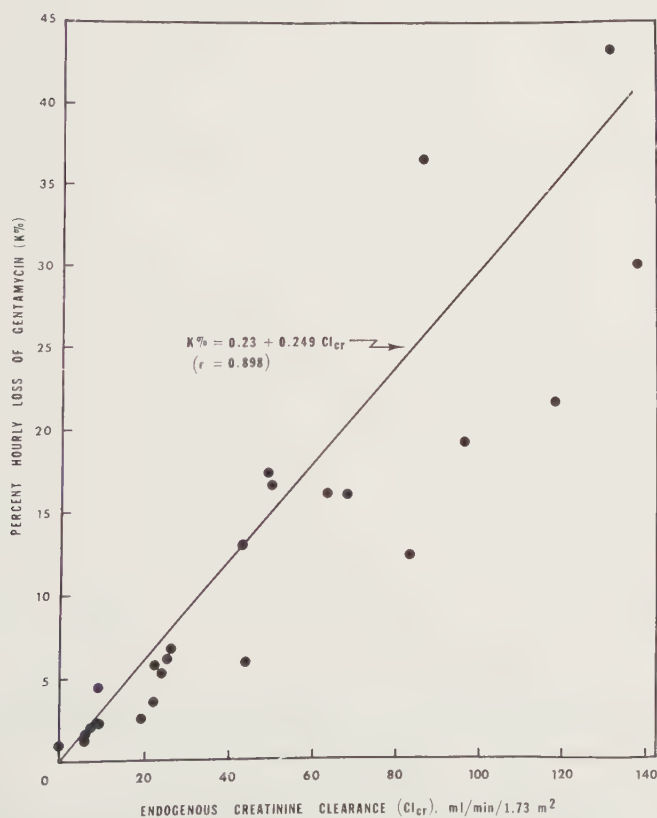


Figure 5. Plot of per cent hourly loss of gentamicin versus endogenous creatinine clearance. The equation shown on the graph corresponds to equation 5 in the text. (Data taken from McHenry et al., 1971.)

To make dosage adjustments when renal function is impaired one uses equation 5.

$$\text{Patient dose} = \text{Normal dose} \times \frac{\text{Patient } K_r}{\text{Normal } K_r} \quad [5]$$

The "patient  $K_r$ " needed to substitute into equation 5 is calculated using equation 3 and the measured value of the endogenous creatinine clearance. The "normal  $K_r$ " value is estimated by means of equation 3 using  $Cl_{cr} = 100$ .

Table 4 lists the  $a$  and  $b$  values and the "normal  $K_r$ " values for 36 drugs, calculated from the data of Dettli et al.<sup>4</sup> Many of the constants in the table were calculated from experimental values in the literature and sometimes the data were poor. Dettli thought that the  $a$  value of 2 in the table for gentamicin is too large and that the value of about 0.2 of McHenry et al.<sup>7</sup> is more nearly correct. Dettli commented to the author that the use of chlortetracycline, methyldigoxin, digitoxin, strophanthin G, strophanthin K, and  $\alpha$ -acetyldigoxin is not recommended in patients with renal failure because nothing is known about the potential pharmacodynamic and toxic activity of metabolites and degradation products of these drugs.

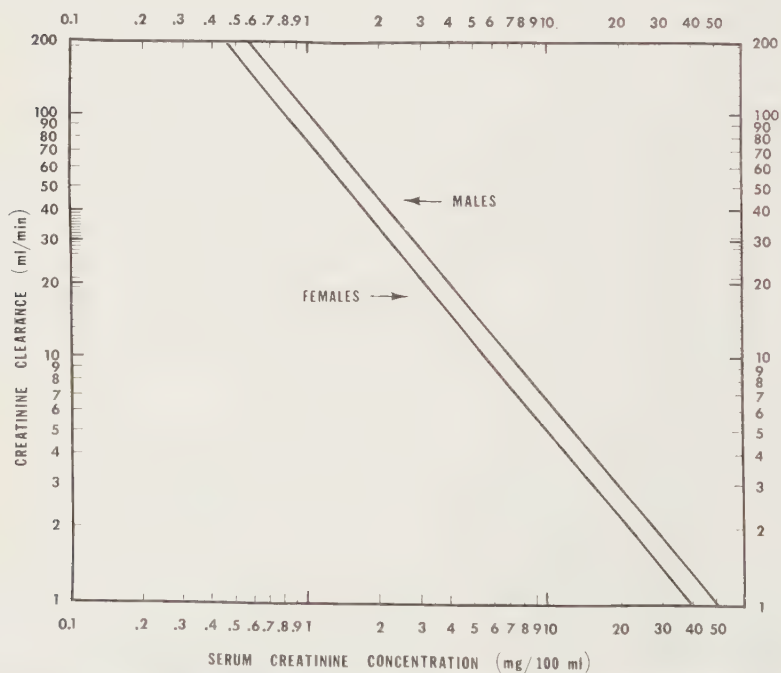


Figure 6. Log-log plot of creatinine clearance versus serum creatinine concentration, based on equation 9, for 98 female patients and 100 male patients at the University Hospital, The University of Michigan. Only the least squares fit lines, and not the individual points, are shown. This plot can be used with a T-square to predict creatinine clearance from serum creatinine concentration.

**Table 3.** *Adjusting Dosage of Drugs in Patients with Impaired Renal Function on Basis of Endogenous Creatinine Clearance*

DRUG	PATIENT $K_{cr} = a + b \cdot Cl_{cr}$ (Per cent per hr.)		NORMAL $K_{cr}$ (Per cent per hr.)	NORMAL $t_{1/2}$ (hr.)
	<i>a</i>	<i>b</i>		
$\alpha$ -Acetyldigoxin	1.	0.02	3.	23.
Ampicillin	11.	0.59	70.	1.
Carbenicillin	6.	0.54	60.	1.2
Cephalexin	3.	0.67	70.	1.0
Cephaloridine	3.	0.37	40.	1.7
Cephalothin	6.	1.34	140.	0.5
Chloramphenicol	20.	0.10	30.	2.3
Chlortetracycline	8.	0.04	12.	5.8
Ciba 36278	3.	0.67	70.	1.0
Colistin	8.	0.23	31.	2.2
Digitoxin	0.3	0.001	0.4	173.
Digoxin	0.8	0.009	1.7	41.
Doxycycline	3.	0.	3.	23.
Erythromycin	13.	0.37	50.	1.4
5-Fluorocytosine	0.7	0.243	25.	2.8
Gentamicin	2.	0.28	30.	2.3
Isoniazid—fast inactivators	34.	0.19	53.	1.3
Isoniazid—slow inactivators	12.	0.11	23.	3.0
Kanamycin	1.	0.24	25.	2.75
Lincomycin	6.	0.09	15.	4.6
Methicillin	17.	1.23	140.	0.5
Methyldigoxin	0.7	0.009	1.6	43.
Oxacillin	35.	1.05	140.	0.5
Penicillin G	3.	1.37	140.	0.5
Polymyxin B	2.	0.14	16.	4.3
Rolitetracycline	2.	0.04	6.	11.6
Streptomycin	1.	0.26	27.	2.6
Strophanthin G	1.2	0.038	5.	14.
Strophanthin K	1.	0.03	4.	17.
Sulfadiazine	3.	0.05	8.	8.7
Sulfamethoxazole	7.	0.	7.	9.9
Sulfasomidine (children)	1.	0.14	15.	4.6
Tetracycline	0.8	0.072	8.	8.7
Thiamphenicol	2.	0.24	26.	2.7
Trimethoprim	2.	0.04	6.	12.
Vancomycin	0.3	0.117	12.	5.8

Patient Dose = Normal Dose  $\times \frac{\text{Patient } K_{cr}}{\text{Normal } K_{cr}}$  = Normal Dose  $\times \frac{a + b \cdot Cl_{cr}}{\text{Normal } K_{cr}}$  where  $Cl_{cr}$  endogenous creatinine clearance in ml. per min.

At University Hospital, if only serum creatinine concentration,  $C_{cr}$ , in mg. per 100 ml. is available, then we can estimate endogenous creatinine clearance from the following equations: For females,  $Cl_{cr} = \text{antilog} [1.8883 - 1.20 \log C_{cr}]$  or use the attached graph. For males,  $Cl_{cr} = \text{antilog} [2.0080 - 1.19 \log C_{cr}]$

Reference for tabled values: Dettli, L., Spring, P., and Ryter, S.: *Acta Pharmacol. (Koh)*, 29 (Suppl. 3):211-224, 1971, and personal communication from Dr. Dettli.

Perrier and Gibaldi<sup>8</sup> stated that creatinine clearance is inversely proportional to the steady state serum creatinine concentration. However, prior to their publication, Wagner<sup>12</sup> had reviewed data from the literature and reported new data showing that the appropriate relationship was as shown in equations K and L of the Appendix—shown graphically in Figure 6. Figure 6 is a log-log plot of creatinine clearance *versus* serum creatinine concentration for 98 female patients and 100 male patients at University Hospital, the University of Michigan. One may use Figure 6 to estimate the endogenous creatinine clearance if only the serum creatinine concentration is known. To obtain a more precise answer, one can use the equations at the bottom of Table 3, which are based on the regression lines shown in Figure 6. Thus, if only the serum creatinine concentration is known one can use Figure 6 or the equations at the bottom of Table 3 to estimate  $Cl_{cr}$ , then substitute this value into equation 3 to obtain the patient  $K_{cr}$ , and then use equation 5 to estimate the patient dose.

#### APPENDIX

The theoretical single dose blood levels in the 0 to 12 hour period, listed in Table 1 under dose 1, were generated by use of general equation A.

$$C(t) = C_0 \left( \frac{k_a}{k_a - K} \right) [e^{-Kt} - e^{-k_a t}] \quad [A]$$

Constants employed were  $C_0 = 100$ ,  $k_a = 1.0445 \text{ hr}^{-1}$  and  $K = 0.17425 \text{ hr}^{-1}$ . Substitution of these constants into equation A yields equation B.

$$C(t) = 120 [e^{-0.17425t} - e^{-1.0455t}] \quad [B]$$

The theoretical single dose blood levels listed were generated by substituting  $t = 0.5, 1, \dots, 12$  hours into equation B.

The line fitted to the points in Figure 1B is the least squares line obtained using the logarithms (base  $e$ ) of the blood levels at 6, 7, 8, 9, 10, 11, and 12 hours with a least squares program and an electronic calculator. The equation of the line obtained was:

$$\ln C = 4.7793 - 0.17348t \quad [C]$$

Equation C may also be written as equation D.

$$C = 119.0 e^{-0.17348t} \quad [D]$$

Hence equation D would give the "line values" of the smooth line which could be drawn through the points in the 6 to 12 hour region of Figure 1A. The bracketed numbers in column 3 under Dose 1 of Table 1 were calculated with the electronic calculator using equation D.

Theoretical blood levels after the sixth dose, for the model employed

in the example, were calculated by means of equations E through G below and are shown in the third column of Table 4. In the fourth column of Table 4 are shown the blood levels predicted in Table 1 in the 30 to 36 hour period after the sixth dose. The accuracy of the superposition method is readily seen. The small deviations are really due to the fact that the elimination rate constant estimated from the data in the 6 to 12 hour region after the single dose, namely  $0.17348 \text{ hours}^{-1}$ , (equations C and D) is somewhat less than the actual elimination rate constant, namely  $0.17425 \text{ hours}^{-1}$ , (equation B above).

$$C(t') = C_0 \left( \frac{k_a}{k_a - K} \right) \left[ \left( \frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}} \right) e^{-Kt'} - \left( \frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a\tau}} \right) e^{-k_a t'} \right] \quad [E]$$

Substituting the same values of  $C_0$ ,  $k_a$ , and  $K$  as shown above, the dose number,  $n = 6$ , and the dosage interval,  $\tau = 6$  hours, followed by simplification yields equation F.

$$C(t') = 184.7e^{-0.17425 t'} - 120.2e^{-1.0455 t'} \quad [F]$$

In equation F,  $t'$  is the time after the sixth dose and is given by equation G,

$$t' = t - (n - 1)\tau \quad [G]$$

where  $t$  is time measured from the first dose,  $n = 6$ , and  $\tau = 6$ .

For the model given in Table 4, the relationship between the loading dose,  $D^*$ , and the maintenance dose,  $D$ , is given by equation H.<sup>6</sup>

$$D^* = \frac{D}{(1 - e^{-K\tau})(1 - e^{-k_a\tau})} \quad [H]$$

Substituting  $K = 0.17425$ ,  $k_a = 1.0455$ , and  $\tau = 6$  into equation H gives equation I.

$$D^* = 1.61D \quad [I]$$

**Table 4.** Comparison of Predicted and Theoretical Blood Levels After Sixth Dose

CLOCK TIME FROM FIRST DOSE (Hours)	TIME AFTER SIXTH DOSE (Hours)	CONCENTRATION	
		Theoretical	Predicted
30	0	64.50	64.53
30.5	0.5	98.02	98.09
31	1	112.9	113.0
32	2	115.5	115.6
33	3	104.3	104.4
34	4	90.16	90.23
35	5	76.64	76.70
36	6	64.70	64.76

Data shown in Figure 4 were generated with equation J.

$$C(t) = A_1 e^{-\alpha t} + A_2 e^{-\beta t} - A_3 e^{-k_a t} \quad [J]$$

where  $A_1 = 50$ ,  $A_2 = 50$ ,  $A_3 = 100$ ,  $\alpha = 0.5$ ,  $\beta = 0.1$ , and  $k_a = 1.5$ .

The relationship between creatinine clearance and serum creatinine concentration is given by<sup>12</sup>

$$Cl_{cr} = Q/C_{cr}^S \quad [K]$$

$$\log Cl_{cr} = \log Q - S \cdot \log C_{cr} \quad [L]$$

where  $Cl_{cr}$  is endogenous creatinine clearance,  $C_{cr}$  is serum creatinine concentration and  $S$  and  $Q$  are constants. The value of the slope factor,  $S$ , is the same for males and females and is 1.1 to 1.3 depending upon the data. The value of  $Q$  is greater for males than females, and this difference is most probably due to the difference in muscle mass between the sexes.

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# **In Vitro Antimicrobial Susceptibility Testing**

## **Clinical Implications and Limitations**

*Thomas L. Gavan, M.D.\**

Successful management of patients with serious bacterial infections is one of the most challenging aspects of clinical medicine today. In large part it depends upon prompt, accurate clinical and microbiological diagnosis, and upon timely institution of appropriate antibacterial therapy. To utilize antibacterial drugs safely and effectively, the clinician must have adequate knowledge of the characteristics of absorption, distribution, metabolism, and excretion of the various agents, as well as an understanding of their mechanisms of action, relative efficacy, and potential side effects. Above all, he must know whether or not the pathogen in question will be inhibited or killed by concentrations of the antibacterial drug that can be safely achieved at the site of infection. Fortunately, for many pathogens the degree of susceptibility to antibacterial drugs can be determined *in vitro*. Furthermore, data are now available suggesting that there is a relationship between the effectiveness of antibiotics against certain bacteria *in vitro* and the outcome of treatment of serious infections caused by those organisms.<sup>1, 9, 10, 15, 21</sup> The purpose of this report is to review selected aspects of the topic of *in vitro* susceptibility testing which may be helpful to the clinician.

Recently Ericsson and Sherries<sup>13</sup> reported the recommendations of the International Collaborative Study Group on Antimicrobial Susceptibility Testing of the World Health Organization. Four categories of susceptibility have been defined. Group 1 includes that degree of *in vitro* bacterial susceptibility that makes *in vivo* response probable when mild to moderately severe systemic infection is treated with the usual dosage of an antimicrobial agent. This group of organisms can be considered susceptible without further qualification. A clinical example of this would be uncomplicated pneumococcal pneumonia which responds to small doses of penicillin G. The second group includes degrees of *in vitro* susceptibility which makes *in vivo* response probable in systemic infection when the

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antimicrobial agent is given in a higher dosage or to the limit of toxicity. A clinical example is pneumococcal meningitis, which requires much larger doses of penicillin G for cure than does uncomplicated pneumococcal pneumonia. The third group includes degrees of in vitro susceptibility which makes in vivo response probable in the treatment of localized infections at sites where the agent can be concentrated by physiologic processes or by local application. An example would be effective management of enterococcal urinary tract infection with a dose of penicillin G inadequate to control infection with this same organism on a heart valve. The fourth group includes those organisms with degrees of in vitro susceptibility which makes in vivo response improbable. This group can be categorically designated as resistant.

It is apparent that laboratory methods for evaluating bacterial susceptibility must relate in some way to practically achievable antimicrobial levels at the infection site. Several such methods are currently available to laboratories. Since in vitro susceptibility tests are performed in order to help clinicians determine which antimicrobial drugs may be effective or ineffective in a particular infection, these tests must be accurate as well as reproducible, not only within a given laboratory, but ideally between laboratories as well. A number of factors may produce significant variation in the results of susceptibility test procedures. These include the size of the bacterial inoculum, the pH of the medium, and incubation time and temperature. Inoculum density is particularly critical. For example, a large number of bacteria usually require a greater dosage of antimicrobial drug for inhibition or killing. Inoculum effect is particularly pronounced when the bacteria involved produce substances capable of destroying the therapeutic agent, such as penicillinase produced by *Staphylococcus aureus*. In this instance, the amount of penicillinase produced by a small inoculum of staphylococci may be insufficient to destroy penicillin G in vitro before it can exert a lethal effect on the growing bacteria, leading to the erroneous conclusion that the organisms were not penicillinase-producers and were thus susceptible to penicillin G. Administration of penicillin G for a serious infection caused by a penicillinase-producing strain of *Staphylococcus aureus* would be ineffective because the usually large numbers of organisms in lesions produce penicillinase in quantities sufficient to destroy the drug. This illustrates the importance of selecting an inoculum representative of conditions existing at the infection site.

The second consideration is the pH at which the test procedure is performed. Many antimicrobial agents are more active at a pH outside the physiologic range. In an assay procedure to measure small quantities of an agent, enhancement of sensitivity by pH adjustment may be desirable; however, in susceptibility testing, pH must be maintained at or near the physiologic level.

Third, incubation time must be reasonable. Inducible enzyme production, such as penicillinase, must be allowed to take place and antimicrobial deterioration must be avoided.<sup>32</sup> These restrictions require that the usual incubation period should not exceed 18 to 24 hours.

## ANTIMICROBIAL SUSCEPTIBILITY TESTING METHODS

In vitro antimicrobial susceptibility testing systems fall into two categories, dilution methods and agar diffusion methods. Dilution methods are inherently quantitative and are preferred especially for patients with serious or life threatening conditions, such as bacterial endocarditis, or for infected patients whose hematologic or immunologic defense mechanisms are impaired. The two tests in this category, broth and agar dilution, differ in the choice of bacteriologic growth medium, liquid or solid. Both procedures are performed as simple two-fold titrations of the antimicrobial agent in the medium of choice. In the broth dilution method a known amount of drug is placed in the first tube and, after subsequent dilution steps and inoculation with the test organism, will yield a series of test tubes containing graduated amounts of the agent spanning the range of concentrations that might be achieved in serum, tissues, or body fluids with conventional doses of the drug. A typical series of eight test tubes might contain 64, 32, 16, 8, 4, 2, 1, 0.5 mcg. per ml., respectively. After inoculation with an appropriate number of bacteria, ( $10^5$  to  $10^6$  per ml.) and incubation overnight at  $35^\circ\text{C}$ , the tubes are examined macroscopically for evidence of growth. The minimum inhibitory concentration (MIC) is read as the least concentration of antimicrobic which inhibits visible growth of the organism. The minimum bacteriocidal concentration (MBC) can be determined with the broth dilution technique by subculturing to an antibiotic free solid medium those tubes that failed to show visible growth. After an additional overnight incubation period, the MBC endpoint is determined as the least concentration of antimicrobial in the original tubes which on subculture proves to be sterile. With bacteriocidal antibiotics there may be no difference, or a difference of one to two dilution intervals, between the MIC and MBC endpoints. With bacteriostatic agents this difference is usually much greater.

Agar dilution methods involve the inoculation of 3 to  $6 \times 10^5$  organisms as droplets on the surface of a series of agar plates containing specific quantities of the antimicrobial being tested. This permits inoculation of a series of test plates containing different concentrations of a single drug with a number of different bacterial isolates. The MIC endpoint is read, as in the broth procedure, as a minimum drug concentration that inhibits visible colonial growth of the organism. The agar dilution method more readily uncovers contamination of the test culture since colonial morphology can be evaluated. In contrast, the MBC endpoint is better determined by the broth method, where the inhibited but potentially viable original inoculum can be subcultured to an antibiotic-free solid medium. Although both methods are time consuming and are usually not available or necessary for routine testing of all clinical isolates, every clinical laboratory should employ one of these methods in those clinical situations requiring quantitative results.

Agar diffusion tests are the methods used most frequently in clinical laboratories engaged in determining antimicrobial susceptibility. Organisms to be tested are inoculated onto the surface of an agar medium and exposed to a diffusion gradient of the antimicrobial agent arising from a

reservoir of some sort, usually a paper disc impregnated with the agent. The dynamics of the diffusion process and its relationship to the growth of the bacterium is complex, and is influenced by the variables mentioned previously.<sup>19</sup> The diameter of the zone of inhibited bacterial growth is determined by the complex relationship between the rate of growth of the organism and rate of diffusion of the antimicrobial through the agar medium away from the impregnated paper disc.<sup>27</sup> An antimicrobial concentration exceeding the MIC of the test bacterial population will inhibit growth until a "critical population" is reached. At this point further bacterial multiplication will be uninhibited.<sup>19</sup> The time required for the organism to reach this "critical population" is called "critical time," and the concentration of antimicrobial in the medium at this time is called the "critical concentration." Variations in the lag phase, of growth generation time of the bacterium, diffusion rate of the antimicrobial in the agar medium, inoculum density, and other factors will effect one or more of these parameters with a resulting variation in the diameter of the inhibition zone. Despite these complexities, reproducible results are attainable when the test conditions are carefully standardized.

Two agar diffusion methods are currently considered satisfactorily standardized for use in clinical laboratories.<sup>14, 25</sup> These are the Kirby-Bauer method<sup>7</sup> and the agar overlay method described by Barry and associates.<sup>3</sup> The Kirby-Bauer method is the more popular of the two. In a recent survey by the College of American Pathologists,<sup>16</sup> 75 per cent of 366 laboratories indicated they were using this single high-content disc method for routine susceptibility testing; an additional 10 per cent used the agar overlay method. Both methods have been specifically designed for routine testing of the susceptibility of common, rapidly growing bacterial pathogens. It must be stressed that the interpretive standards used with these methods are not applicable to the study of slowly growing organisms or to those that require special growth conditions, such as an extensively supplemented medium, a carbon dioxide atmosphere, or anaerobic conditions. In practice, these tests are limited to members of the family *Enterobacteriaceae*, *Pseudomonas* sp., *Staphylococcus* and the common pathogenic streptococci.

These methods specify the use of Mueller-Hinton agar medium for routine susceptibility testing. It shows good batch reproducibility, provides adequate growth factors for most bacteria, and is relatively free from sulphonamide inhibitors. With certain streptococci, 5 per cent defibrinated sheep blood may be added to this medium to insure satisfactory growth, without altering the interpretation of the test. The bacterial inoculum is prepared and standardized in the Kirby-Bauer method by touching a wire loop to the tops of four or five colonies of the test organism and transferring this growth to 4 to 5 ml. of a suitable broth medium such as soy bean casein digest. After a growth period of 2 to 5 hours, the turbidity and thus the inoculum density is adjusted with sterile saline or broth to the turbidity of a barium sulfate standard (MacFarland 1/2). The adjusted bacterial suspension (approximately  $10^8$  organisms per ml.) is then inoculated over the entire surface of a 150 × 15 mm. Mueller-Hinton agar plate with a cotton swab. Discs containing specified amounts of the antimicrobial agents to be tested are firmly pressed into contact with the

inoculated agar surface and the plates incubated at 35° C. for 14 to 18 hours. After the incubation period, zones of bacterial inhibition surrounding the discs are measured with calipers or a ruler, and these measurements are compared with the interpretive chart shown in Table 1.

The agar overlay method of Barry differs from the Kirby-Bauer procedure mainly in the method of preparation of the standardized inoculum. This method utilizes the principle that an organism inoculated in large numbers into a liquid medium of comparatively small volume will reach the stationary phase of the growth cycle in a matter of a few hours. The growth from 4 to 5 colonies is used to prepare a visibly turbid suspension in 0.5 ml. of brain heart infusion broth, which is then incubated at 35 to 37° C. in a water bath or heating block for at least 4 hours, but not longer than 8 hours. Using a calibrated platinum loop, 0.001 ml. of this culture is transferred to 9 ml. of a 1.5 per cent aqueous solution of agar at 45 to 50° C., mixed well, and distributed evenly over the surface of a Mueller-Hinton agar plate in a 150 by 15 mm. petri dish. The overlay of agar, uniformly seeded with the test organism, is allowed to solidify for a few moments and the antimicrobial containing discs are then applied as described previously. The same interpretive criteria used with the Kirby-Bauer method can be applied to the agar overlay technique.

The interpretive criteria that have been established for these methods are a most significant contribution to clinical laboratory practice. These criteria were developed over a number of years, most notably by investigators at the University of Washington, Seattle.<sup>4,6, 8, 20, 26</sup> When studying a large number of bacterial isolates, the inhibitory zone produced by standardized tests such as those described above can be related to the MIC as measured by an agar or broth dilution susceptibility test. An inverse linear relationship exists between these two variables for many antimicrobial agents and rapidly growing bacterial species. The larger the inhibitory zone, the smaller the corresponding MIC, and vice versa. In view of this relationship, criteria for test interpretation have been developed which relate the inhibitory zone diameter indirectly to the MIC and thus to achievable drug levels (Table 1). Three categories of susceptibility are defined. "Susceptible" implies that an infection due to the strain tested can be expected to respond to the recommended dosage of antimicrobial for that type of infection and infecting species. Resistant strains, on the other hand, are not completely inhibited by concentrations within the therapeutic range. The intermediate category includes strains which may respond to concentrations attainable by unusually high dosage, or to strains which may be eradicated from the urinary tract, or similar sites, where the antimicrobial is concentrated. The intermediate category also comprises a "buffer zone" to prevent significant interpretive discrepancies resulting from small, uncontrolled technical factors.

With some antimicrobials, such as tetracycline, the distribution of inhibitory zone diameters is bimodal. Two populations of organisms are observed, those with small inhibitory zones and those with much larger zones, with relatively few examples between these extremes. In such cases, the two populations represent those resistant to the drug (smaller zones) and those susceptible (larger zones). An example of this bimodal

Table 1. Zone-Size Interpretive Standards and Approximate MIC Breakpoints for the Disc Diffusion Technique<sup>a</sup>

ANTIMICROBIAL AGENT	DISC POTENCY	INHIBITORY ZONE DIAMETER (to nearest mm)			APPROX MIC BREAKPOINT	
		Resistant	Intermediate	Susceptible	Resistant	Susceptible
Penicillin G and Ampicillin	10 units 10 µg.	20 or less 11 or less 11 or less	21-28 12-13 12-21	29 or more 14 or more 22 or more	Penicase <sup>b</sup> ≥ 32 µg./ml. ≥ 32 µg./ml.	≤ 0.1 µg./ml. ≤ 5-15 µg./ml. <sup>c</sup> ≤ 1.5 µg./ml.
Staphylococci						
Enterobacteriaceae and Enterococci						
Other organisms						
Methicillin	5 µg.	9 or less	10-13	14 or more		≤ 2.5 µg./ml.
Nafcillin or Oxacillin	1 µg.	10 or less	11-12	13 or more		≤ 0.6 µg./ml.
Vancomycin	30 µg.	9 or less	10-11	12 or more		≤ 5 µg./ml.
Cephatholin	30 µg.	14 or less	15-17	18 or more	≥ 32 µg./ml.	≤ 10 µg./ml.
Cephalexin	30 µg.	11 or less	12-15	16 or more	≥ 40 µg./ml.	≤ 10 µg./ml.
Carbenicillin	50 µg.					
<i>Pseudomonas</i> sp		12 or less	13-14	15 or more	≥ 250 µg./ml.	≤ 125 µg./ml.
<i>Proteus</i> and <i>E. coli</i>		17 or less	18-22	23 or more	≥ 32 µg./ml.	≤ 16 µg./ml.
Polymyxin B <sup>d</sup>	300 units	8 or less	9-11	12 or more	≥ 50 units/ml.	
Chloramphenicol	30 µg.	12 or less	13-17	18 or more	≥ 25 µg./ml.	≤ 12.5 µg./ml.
Tetracycline	30 µg.	14 or less	15-18	19 or more	≥ 12.5 µg./ml.	≤ 4 µg./ml.
Erythromycin	15 µg.	13 or less	14-17	18 or more	≥ 8 µg./ml.	≤ 2 µg./ml.
Lincomycin	2 µg.	9 or less	10-14	15 or more	≥ 8 µg./ml.	≤ 2 µg./ml.
Clindamycin	2 µg.	11 or less	12-15	16 or more	≥ 8 µg./ml.	≤ 2 µg./ml.
Kanamycin	30 µg.	13 or less	14-17	18 or more	≥ 25 µg./ml.	≤ 6 µg./ml.
Neomycin	30 µg.	12 or less	13-16	17 or more	≥ 15 µg./ml.	≤ 6 µg./ml.
Streptomycin	10 µg.	11 or less	12-14	15 or more	≥ 12.5 µg./ml.	≤ 6 µg./ml.
Gentamicin	10 µg.	12 or less	13-14	15 or more	> 35 mg.% <sup>d</sup>	≤ 10 mg.% <sup>d</sup>
Sulfonamides <sup>e,f</sup>	300 µg.	12 or less	13-16	17 or more	> 100 µg./ml.	≤ 25 µg./ml.
Nitrofurantoin <sup>f</sup>	300 µg.	14 or less	15-18	19 or more	> 12.5 µg./ml.	≤ 12.5 µg./ml.
Nalidixic Acid <sup>g</sup>	30 µg.	13 or less	14-18	19 or more		

<sup>a</sup>As modified from Bauer et al. (1968). Prepared by NCCLS Subcommittee on Antimicrobial Susceptibility Testing.<sup>25</sup>

<sup>b</sup>Penicillinase-producing staphylococci.

<sup>c</sup>MIC dependent upon dilution method used.

<sup>d</sup>Polymyxin B diffuses poorly in agar and the accuracy of the diffusion method is thus less than with other antibiotics. Resistance is always significant, but when treatment of systemic infections due to susceptible strains is considered, it is wise to confirm the results of a diffusion test with a dilution method.

<sup>e</sup>300 µg. or 250 µg. sulfonamide discs can be used with the same standards of zone interpretation (MIC values are for sulfamethizole).

<sup>f</sup>Urinary tract infections only.

PERCENT DISTRIBUTION OF INHIBITION ZONE DIAMETER  
*S. AUREUS* ISOLATES (115 STRAINS)

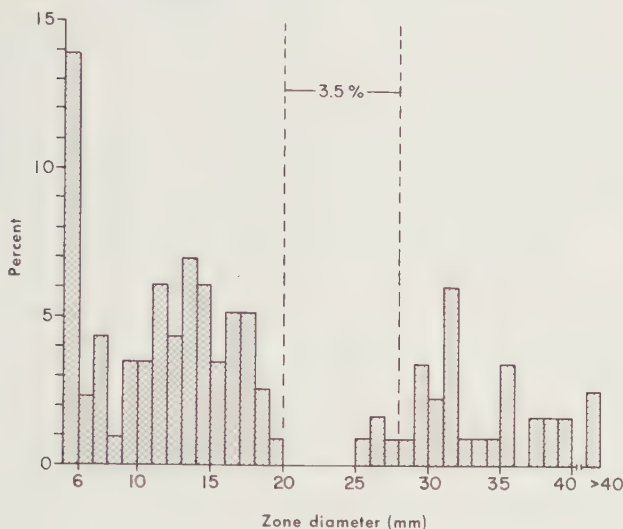


Figure 1. Zone sizes of 115 strains of *S. aureus* illustrating the bimodal nature of their distribution.

pattern using *S. aureus* and penicillin G is illustrated in Figure 1. Isolates with smaller zones of inhibition can be shown to produce penicillinase. Those with larger zones do not. Assignment of organisms into susceptible and resistant categories can therefore be easily based on this type of distribution of inhibitory zones.

The interpretive criteria used with these standardized tests have been developed in relationship to achievable blood levels of the majority of antimicrobials concerned. The exception is for nitrofurantoin and naladixic acid, where urine levels were used, since significant blood levels are not attainable. Stamey et al.<sup>28</sup> proposed that separate criteria for susceptibility of organisms causing urinary tract infection be defined in terms of urine levels of the antimicrobial even for drugs where therapeutic levels in serum are readily attainable. To date, this suggestion has not been pursued.

## INDICATIONS FOR ANTIMICROBIAL SUSCEPTIBILITY TESTS

Antimicrobial susceptibility testing is indicated when pathogens with unpredictable susceptibility patterns are isolated from meaningful sites of infection from patients who require antimicrobial therapy. Those organisms considered part of the "normal flora," particularly of the upper respiratory tract, nasopharynx, nose, and stool, should not be tested when isolated from specimens obtained from these sites. Organisms with predictable susceptibility patterns likewise do not require routine testing. Pneumococci, group A streptococci, and meningococci are examples. On

the other hand, organisms such as the Enterobacteriaceae, *S. aureus*, and enterococci, which include a significant percentage of resistant strains, should be tested when isolated in significant numbers from adequate clinical specimens. Organisms likely to become resistant should be tested to detect emerging resistance. Epidemiologic information obtained through susceptibility testing can also be of value in the evaluation of nosocomial infections.

Susceptibility tests performed on plates inoculated directly with pathologic material should be discouraged. This method is seldom standardized, more than one organism may be present, and the overgrowth of normal flora or other contaminating organisms may give the appearance of resistance. Direct susceptibility tests can be justified only in cases of real clinical emergency, and then only when direct Gram stain suggests the presence of a single pathogen. In all such cases, the direct test should be viewed only as preliminary or interim information and the test repeated using a standardized technique.

The indications and contraindications for quantitative agar and broth dilution tests are generally the same as those for diffusion tests; however, they are most useful in cases of bacterial endocarditis, and in patients with severe systemic infections in whom there is failure to respond to what should be adequate therapy. They are also useful in patients with severe infections who are being treated with potentially toxic drugs or who otherwise have impaired cellular or humoral defense mechanisms. Because of their complexity and expense, widespread, routine application of these quantitative methods has not been achieved. The introduction of semi-automation, however, promises to make these tests more accessible to the clinical laboratory in the future.<sup>17, 22, 23, 29</sup>

## SELECTION OF ANTIMICROBIAL AGENTS FOR TESTING

To simplify the routine susceptibility test, the number of drugs tested must be limited. It is unreasonable to expect the microbiologist to test every available agent and its analogues against every organism isolated. From a practical standpoint, 10 to 12 drugs can be tested simultaneously by the disc diffusion methods described. Using semi-automated devices, up to eight agents can be tested simultaneously by the broth dilution method. It becomes important, therefore, to select a battery of agents that is representative of those categories of drugs currently known to be effective, without duplication of agents and with essentially the same spectrum of antibacterial activity. The following guidelines may be used in selecting agents to be used.<sup>14, 18, 25</sup>

### Penicillins

It is advisable to test all staphylococci against penicillin G (penicillinase labile) and against one penicillinase-stable drug such as methicillin, oxacillin, or nafcillin. Neither cloxacillin nor dicloxacillin should be used for this purpose, because they fail to detect certain hetero-resistant strains. When testing with methicillin the incubation temperature should not exceed 35° C., or hetero-resistance may not be detected.<sup>12</sup> In addition, ampicillin should be tested with gram-negative bacilli. There is no reason

to include ampicillin in tests with staphylococci because of its lesser in vitro activity and similar susceptibility to penicillinase as compared to penicillin G. It may be useful to test carbenicillin against certain gram-negative bacilli, especially *Pseudomonas* sp.

### Cephalosporins

Of the currently available cephalosporanic acid derivatives, only cephalothin needs to be tested routinely. However, testing with other cephalosporins may be indicated for the occasional gram-negative bacillus that appears resistant to cephalothin, when alternative drugs are unsatisfactory. Cephaloridine should not be tested against staphylococci because of its increased susceptibility to penicillinase.<sup>2, 30</sup>

### Tetracyclines

Drugs in this group are closely related and only tetracycline hydrochloride need be tested routinely. Exceptions are quite rare.

### Polymyxins

Polymyxin B and polymyxin E (colistin) are closely related and only one needs to be tested routinely. These drugs diffuse poorly in agar and the reliability of a diffusion method is less than with other antibiotics. The demonstration of in vitro resistance is always a significant finding, but when treatment of a systemic infection caused by apparently susceptible organisms is being considered, it is wise to confirm the results with one of the dilution methods.

### Aminoglycosides

This group of chemically related drugs includes kanamycin, neomycin, streptomycin, and gentamicin. Their relationship, however, is not complete enough to assure that an organism resistant or susceptible to one will be equivalently resistant or susceptible to another. Streptomycin is now indicated chiefly for the treatment of tuberculosis, bubonic plague, tularemia, and enterococcal endocarditis, the latter in conjunction with penicillin. Routine testing of streptomycin is therefore not indicated. Neomycin has limited application, and routine testing is not required. Gentamicin, in addition to having a broad spectrum against the *Enterobacteriaceae*, is also effective against *Pseudomonas aeruginosa*, and should be tested routinely.

### Macrolides

Erythromycin is the most widely used drug in this category and should be considered for use in testing gram-positive cocci. The related drug oleandomycin does not share complete cross resistance with erythromycin and may be included for testing if its use is anticipated.

### Lincomycin Group

Either lincomycin or clindomycin may be tested routinely, but not both.

### Chloramphenicol

Chloramphenicol is a widely used antibiotic with a range of activity against gram-positive and gram-negative organisms as well as certain

mycoplasma and rickettsiae. In general, gram-negative organisms have remained highly susceptible, but susceptibility has been a variable phenomenon and wide variations appear. Chloramphenicol may be useful for treatment of serious infections caused by susceptible strains of *Salmonella*, *Bacteroides*, *Haemophilus influenzae*, and other pathogens, particularly when no safe, effective alternative agent is available.

### Sulfonamides

Susceptibility testing with these antimicrobial agents presents problems. Because of the difficulty in obtaining a medium reproducibly free of para-aminobenzoic acid, a sulfonamide inhibitor interpretation of in vitro tests is frequently misleading.<sup>11</sup> In some instances, as many as 61 per cent of bacterial strains shown to be resistant in vitro have responded favorably clinically.<sup>21</sup> In these instances, clinical judgment proved to be a better guide to therapy than the results of in vitro tests. Unless a medium free of para-aminobenzoic acid can be reliably obtained and used, sulfonamide testing is not recommended as a routine procedure.

### Naladixic Acid, Nitrofurantoin, and Methenamine Mandelate

These agents yield relatively low blood levels when given by mouth, but are highly concentrated in the urine. Routine susceptibility tests are indicated only with organisms isolated from infections of the urinary tract. In vitro tests with methenamine mandelate should not be performed because the activity of this drug in vivo depends on the attainment of a urinary pH of 5.0 or less, and in vitro test conditions may bear no relationship to the situation in the urine—the only possible site of antibacterial activity in the patient.<sup>31</sup>

## CONCLUSION

An attempt has been made to provide the reader with a brief review of the current status of antimicrobial susceptibility testing. The underlying principles and methods of performance of these tests have been outlined, and the comparative advantages and disadvantages have been pointed out. As with the results of any laboratory test procedure, the end-point observed in a susceptibility test, be it the inhibitory zone diameter, the MIC or the MBC, should not be the sole determining factor for the selection of the most appropriate antibacterial agent. The laboratory provides a single datum that can be added to the physician's knowledge of his patient, and his knowledge of the available drugs, in order to serve as an aid in selecting the appropriate therapy.

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## Antibiotics for Treatment of Infections Caused by Gram-Positive Cocci

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Gram-positive coccal infections still present complex and difficult therapeutic problems, despite the fact that they have received relatively little attention in the recent literature. The purpose of this paper is to outline an approach to the antimicrobial therapy of these infections. Limitations of space and the frequent lack of wholly satisfactory data comparing the efficacy of alternative regimens dictate an approach that is necessarily arbitrary and selective. Hopefully, however, the material presented will aid the clinician in devising rational therapy for these commonly encountered infections.

### THE PENICILLINS

Penicillins remain the mainstay of treatment of gram-positive coccal infections. These drugs exemplify the principle of *selective toxicity*, which is a major goal in the choice of a chemotherapeutic agent. Selective toxicity refers to a mechanism of action which exploits a biologic difference between bacterial cells and mammalian cells. Penicillins act by interfering with bacterial cell wall synthesis,<sup>20</sup> a process which does not take place in mammalian cells. As a result, the penicillins have remarkably little direct toxicity to the host over a wide range of dosage.

Penicillin G (benzyl penicillin) was the first antibiotic to be used clinically, and it remains one of the most useful ones today. Despite long and extensive use of the drug, pneumococci and group A streptococci have remained uniformly sensitive to low concentrations of penicillin G. Resistance to penicillin G has become common among staphylococci, however, and has limited the usefulness of penicillin G in the treatment of staphylococcal infections.<sup>25</sup> This problem has stimulated the development of a number of semisynthetic penicillin compounds which resist inactivation by staphylococcal penicillinase, the most common cause of penicillin-resistance in staphylococci.<sup>14</sup>

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**Table 1.** *Some Properties of Various Penicillins Effective in Gram-Positive Infections*

SIDE CHAIN	GENERIC NAME	ORAL ABSORPTION	PENICIL- LINASE- RESISTANT	ALLER- GENICITY*	AVAILABLE FORMS
Benzyl	Penicillin G	Variable	No	Yes	O, IM, IV
Phenoxymethyl	Penicillin V	Yes	No	Yes	O
Phenoxyethyl	Phenethicillin	Yes	No	Yes	O
Aminobenzyl	Ampicillin	Yes	No	Yes (highly)	O, IM, IV
Dimethoxybenzyl	Methicillin	No	Yes	Yes	IM, IV
Isoxazolyl	Oxacillin	Variable	Yes	Yes	O, IM, IV
	Cloxacillin	Yes	Yes	Yes	O
	Dicloxacillin	Yes	Yes	Yes	O, IM
Ethoxynaphthamido	Nafcillin	Variable	Yes	Yes	O, IM, IV

\*With the exception of ampicillin, orally administered penicillins appear to have less tendency to cause sensitization than do those given parenterally.

The basic nucleus that is common to all the penicillins is 6-aminopenicillanic acid. A particularly important part of the penicillin nucleus is the beta-lactam ring. Unless the beta-lactam ring is intact, the compound has insignificant antibacterial activity. Staphylococcal penicillinase or beta-lactamase hydrolyses the beta-lactam ring and thus inactivates the penicillin.<sup>25</sup>

The various penicillins differ only in the nature of the side chain attached to the 6-aminopenicillanic acid nucleus. Some of these side chains, and the properties they confer on the resulting penicillin compounds, are shown in Table 1. In the case of penicillin G, the side chain is a benzyl group. When phenoxymethyl and phenoxyethyl side chains are substituted, penicillin V and phenethicillin are obtained. These compounds have the same antibacterial spectrum as penicillin G. Their sole advantage over penicillin G is their greater stability in acid solutions, which results in greater and more reliable absorption after oral administration. Although both are effective, phenethicillin is more expensive and less often used than is penicillin V.

When certain bulky side chain groups are substituted in the penicillin molecule, the ability of staphylococcal penicillinase to hydrolyse the beta-lactam ring is greatly inhibited. Such side chains characterize the semisynthetic penicillinase-resistant penicillins which have become the mainstay of treatment of resistant staphylococcal infection.<sup>14</sup> It is thought that the bulky side chains change the three-dimensional structure of the molecule in such a way that it does not fit into the active site of staphylococcal penicillinase.

Other side chain substitutions result in penicillins with increased activity against certain gram negative organisms. These compounds, such as ampicillin and carbenicillin, also retain activity against most of the same organisms which are affected by penicillin G. In common with penicillin G, they are not effective against penicillinase-producing staphylococci. In general, the gram-positive activity of these semisynthetic

penicillins is less than that of penicillin G on a weight basis, so that they usually are not indicated in the treatment of known gram-positive coccal infections.

### Penicillin G

Penicillin G is available in several forms for parenteral administration. *Aqueous penicillin G* is soluble and can be given intramuscularly or intravenously. It provides the highest peak blood levels of any penicillin G preparation, but its serum half-life is short and several injections must be given each day. It should be noted, however, that effective tissue levels persist longer than do serum levels,<sup>27</sup> so that, except in meningitis, injections more frequent than every 6 hours usually are not necessary. Aqueous penicillin G is indicated in the treatment of relatively severe infections, and in infections caused by organisms not highly sensitive to penicillin G.

*Procaine penicillin G* consists of penicillin G combined with procaine on a mole-for-mole basis. Its low aqueous solubility causes it to be released much more slowly after intramuscular injection, so that blood levels persist for 12 to 24 hours after a single administration. The prolonged blood levels are convenient since they permit reduction in the number of injections, often to as few as one per day. Peak blood levels, however, are only a small fraction of those obtained with an equivalent amount of aqueous penicillin G. Thus, procaine penicillin G is appropriate only for infections of mild to moderate severity caused by highly sensitive organisms, such as the pneumococcus and group A streptococcus.

*Benzathine penicillin G* (Bicillin) is released extremely slowly from the site of injection, with detectable blood levels persisting for 3 to 4 weeks. As would be expected, peak blood levels are extremely low, so that this preparation ordinarily is not useful in the treatment of acute infections, with the exception of pharyngitis caused by the highly penicillin-sensitive group A streptococcus. Benzathine penicillin G is effective prophylactically in the prevention of group A streptococcal infection in patients with rheumatic heart disease. It is important to note that the low blood penicillin levels obtained with benzathine penicillin G will *not* protect such patients from bacterial endocarditis caused by viridans streptococci, enterococci, or other organisms. The drug also is useful in the treatment of syphilis, where prolonged, low blood levels are effective. A significant disadvantage of benzathine penicillin G is that when an allergic reaction occurs, its manifestations may persist for several months. Such prolonged reactions frequently are of the serum sickness type.

### Semisynthetic Penicillinase-Resistant Penicillins

These penicillins are effective against penicillinase-producing staphylococci and have useful activity against other gram-positive cocci, with the notable exception of the enterococcus. Their degree of activity against penicillin G-sensitive organisms is generally less than that of penicillin G. Thus, penicillinase-resistant penicillins should not be used to treat infections known to be caused by organisms sensitive to penicillin G. Strains of staphylococci resistant to this group of semisynthetic

penicillins have been identified<sup>3, 4, 10</sup> and such organisms have become a major problem in Europe. Fortunately, such staphylococci are as yet quite uncommon in the United States.

The various penicillinase-resistant penicillins vary in their activity on a weight basis and in their rates of hepatic inactivation and renal clearance.<sup>9, 22</sup> These differences are offset to some extent by differences in the extent of plasma protein-binding. The clinical implications of these variables are not entirely clear and any of the drugs can be used effectively if given in sufficient dosage. When oral administration is indicated, we employ dicloxacillin because of its efficient absorption and the high blood levels obtained.<sup>9, 22</sup> Cloxacillin also is a very effective oral agent. Oxacillin and nafcillin can be used orally, but their absorption is somewhat less reliable. Methicillin, oxacillin, dicloxacillin and nafcillin all can be used effectively by parenteral administration. Methicillin is less potent on a weight basis,<sup>11</sup> and larger doses (12 to 18 gm. per day) should be used in treating serious staphylococcal infections. In contrast, 8 to 12 gm. of the other penicillinase-resistant penicillins usually is sufficient. Renal excretion of methicillin is very rapid, so that more frequent administration (every 3 or 4 hours) is required. In addition, when treating suspected gram-positive coccal infection before drug sensitivity data are known, many clinicians give penicillin G in addition to methicillin. This probably is not necessary when one of the other penicillinase-resistant penicillins is employed.

### Allergic Reactions to Penicillins

Allergic reactions are the most commonly encountered type of adverse reaction associated with penicillin therapy. Such reactions customarily are classified as *immediate* (onset within the first hour), *accelerated* (onset between one and 48 hours), and *delayed*. Immediate reactions, in general, are the most serious, and include anaphylaxis, angioneurotic edema, and urticaria. Accelerated reactions include laryngeal edema, urticaria, rash, and fever. Delayed reactions are manifested by rashes, fever, urticaria, or the syndrome of serum sickness. Fortunately, life-threatening reactions are rare.<sup>17</sup> Rashes and urticarial reactions, however, are responsible for considerable morbidity and patient discomfort. Drug fevers, which may present without any other obvious evidence of allergy, pose a frequent diagnostic dilemma. One of the most serious aspects of the problem is the fact that patients with a history of penicillin allergy who subsequently develop infections often must be treated with an inferior drug.

With most penicillins, the incidence of recognizable allergic reactions is about 2 to 5 per cent. Ampicillin is an exception, the incidence of allergic reactions with this drug being perhaps twice as great.<sup>23</sup> Skin rashes form the bulk of such reactions, and life-threatening reactions may be no more common than is the case with other penicillins. It is by no means certain that all patients developing allergic reactions to ampicillin would again react adversely if subsequently given other penicillins. Although allergic cross-reactivity among the various penicillin derivatives is not universal, it is very common, and for practical purposes a person reacting to one penicillin must be considered allergic to all peni-

cillins. In the treatment of infections known or likely to be caused by gram-positive bacteria other than the enterococcus, ampicillin should not be used, since it offers no advantage and is associated with a greater frequency of allergic reactions.

When patients report a history of penicillin allergy, it usually is possible to select an effective substitute drug. Outpatients with such a history almost always should receive another antibiotic. Occasionally, however, in the hospital treatment of serious infections such as bacterial meningitis or endocarditis, penicillin is clearly superior to any available substitute. In such situations, it is of urgent importance to determine whether the administration of penicillin would be likely to provoke a life-threatening allergic reaction.

Anaphylactic and accelerated urticarial reactions to penicillin are mediated by IgE skin-sensitizing antibodies to penicillin degradation products.<sup>16, 17</sup> It has been shown that negative skin tests to both of two antigenic materials, benzylpenicilloyl polylysine and minor determinant mixture, virtually exclude the possibility of an immediate allergic reaction to penicillin.<sup>16, 17</sup> Skin tests are not of value in predicting delayed skin eruptions, which are usually related to the presence of IgM antibodies.<sup>16</sup>

Unfortunately, neither benzylpenicilloyl polylysine nor minor determinant mixture is as yet generally available. Skin testing with unaltered penicillin G is not reliable in excluding anaphylactic hypersensitivity. Thus, at present, one must rely primarily on clinical criteria in deciding whether to attempt penicillin therapy. A careful and detailed history of the nature of the alleged penicillin reaction is of great importance. The date of the reaction also is significant, since the likelihood of an immediate reaction on rechallenge appears to decline with time. If the reaction was minor or questionable, and especially if it occurred long ago, the cautious administration of penicillin is sometimes justified. This always should be undertaken in the hospital, with appropriate emergency measures readily available.

Patients with a history of well documented penicillin allergy are occasionally felt to have a critical need for penicillin therapy. If the reaction was immediate and recent, administration of penicillin is too dangerous and should not be attempted. If the nature of the reaction was less serious, or if the reaction was not recent, "desensitization" can be undertaken. This involves the sequential administration of increasing quantities of penicillin, beginning with a minute dose. Antihistamines are often administered during this procedure. Although the exact immunologic mechanisms which occur during "desensitization" are uncertain, it usually can be accomplished successfully, but it is time-consuming and potentially hazardous. It should be attempted only by a physician experienced in the technique.

## ALTERNATIVES TO THE PENICILLINS

Other drugs used in treating infections caused by gram positive cocci properly are considered penicillin substitutes. Their main indications are in patients who are suspected of allergy to penicillin and, to some extent, in treating infections in which the causative organism is uncertain.

## Cephalosporins

The cephalosporins frequently are employed as substitutes for penicillin. These drugs, which are chemically similar to the penicillins, appear to act by the same mechanism, that is, by interfering with cell wall synthesis.<sup>5</sup> They are active against most gram-positive cocci, including penicillinase-producing staphylococci.<sup>29, 30</sup> A notable exception is the enterococcus, against which the cephalosporins are ineffective. Cephalosporins also have activity against a number of gram-negative organisms, including *Proteus mirabilis*, most *Klebsiella*, and the majority of *E. coli*.<sup>29, 30</sup>

The cephalosporins have no advantage over the appropriate penicillin in treating gram-positive bacterial infections unless the patient is thought to be allergic to penicillin. They are frequently useful in such allergic patients, but immunologic cross-reactions do occur. Such cross-reactions are apparently rare;<sup>29</sup> we have not observed a definite example in a large number of patients with a history of penicillin allergy treated with cephalothin. Primary hypersensitivity to the cephalosporins resembles penicillin allergy, and occurs with approximately the same frequency.<sup>29</sup>

The various cephalosporins have essentially the same spectrum of antibacterial activity, but vary considerably in their in vitro activity on a weight basis. Each of the drugs has its own particular advantages and disadvantages which should be kept in mind in the choice of a preparation.

*Cephalothin* is quite active and relatively nontoxic, but its local irritative properties are a problem. It is a frequent cause of phlebitis when given intravenously. Intramuscular injection causes so much pain that this route of administration probably should not be used. Cephalothin crosses the blood-brain barrier poorly<sup>18</sup> and should not be used in infections of the central nervous system. Cephalothin has not been shown definitely to be nephrotoxic, although possible nephrotoxicity has been noted in a few patients receiving extremely large doses. Serious renal injury has been noted, however, in a small number of patients receiving the combination of cephalothin and gentamicin.<sup>7</sup>

*Cephaloridine* is even more active than cephalothin on a weight basis. In addition, it is much less irritating and can be given by intramuscular injection. It penetrates the central nervous system more reliably than does cephalothin, and it has been used successfully as an alternative to penicillin in treating pneumococcal meningitis. Unfortunately, it has the potential for causing serious renal tubular injury, and in patients with normal renal function the dose must not exceed 4 gm. per day. Its use in persons with reduced renal function is extremely hazardous and should be avoided. It may be useful, however, in persons without renal function being maintained on chronic dialysis.<sup>21</sup>

*Cephalexin* is well absorbed from the gastrointestinal tract, and is available only for oral use. Although high blood levels can be obtained, the drug is much less active on a weight basis than are cephalothin or cephaloridine.<sup>29</sup> The principal indication for the drug seems to be in the treatment of selected urinary tract infections. Its use as "step-down"

therapy in patients recovering from systemic infections initially treated with cephalothin or cephaloridine is not recommended.

*Cefazolin*, a new parenteral cephalosporin,<sup>8, 12</sup> was released for general use just as this article went to press. Cefazolin is reported to be effective clinically in doses of 2 to 4 gm. per day, and to be less locally irritating than cephalothin, so that intramuscular administration is feasible. Blood levels are both higher and more prolonged than those obtained with equal doses of cephalothin or cephaloridine. This advantage may be offset somewhat by greater protein binding of cefazolin. Nephrotoxicity has not been described to date. Although the early reports seem promising, further clinical experience will be needed to clarify the choice between cefazolin and the previously available cephalosporins.

### Erythromycin

Erythromycin is a useful substitute for penicillin in the treatment of gram-positive coccal infections, particularly when oral administration is feasible, that is, in infections of mild to moderate severity. It is active against streptococci, pneumococci, and many but not all strains of staphylococci. Most strains of enterococci also are inhibited by erythromycin. Since erythromycin is also active against *Mycoplasma pneumoniae*, it may be useful in patients with pneumonia in whom the differentiation between mycoplasmal and pneumococcal infection cannot be made with certainty.

In most instances erythromycin should be given orally, since the parenteral form is extremely irritating. Of the several oral forms available, erythromycin estolate is absorbed better and gives higher blood levels than erythromycin stearate or erythromycin base.<sup>11</sup> Whether the higher blood levels obtained with erythromycin estolate are associated with greater success in treatment of infections is unclear on the basis of the few data currently available.

In an occasional patient, erythromycin estolate has been associated with cholestatic hepatitis, apparently the result of hypersensitivity to the drug.<sup>2</sup> This is reversible upon withdrawal of the drug, and persistent hepatic dysfunction has not been reported. The symptoms are unpleasant, however, and a few patients have been subjected to unnecessary surgery because of the erroneous diagnosis of acute cholecystitis or cholangitis. Whether the better absorption of erythromycin estolate confers sufficient advantage to justify the possibility of this adverse reaction is a question that is difficult to resolve on the basis of the data available.

Erythromycin is largely concentrated in the liver and excreted into the bile. The dose need not be reduced in patients with renal insufficiency. The drug probably should be avoided in patients with severe liver disease.

### Lincomycin and Clindamycin

Lincomycin and clindamycin, which is 7-chlorolincomycin, resemble erythromycin in their antibacterial spectrum and mechanism of action.<sup>19</sup> Despite this, they are chemically dissimilar to erythromycin, and cross-

sensitization apparently does not occur. The lincomycins are active against group A streptococci, pneumococci, and most strains of staphylococci. Enterococci are resistant to the lincomycins. Clindamycin is considerably more active than lincomycin on a weight basis.<sup>19</sup>

Lincomycin is incompletely absorbed from the gastrointestinal tract and commonly causes diarrhea, which may be quite severe. Clindamycin is much more completely absorbed and is well tolerated by most patients. It recently has been recognized, however, that oral clindamycin can be associated with severe and protracted colitis.<sup>6</sup> This can be very severe, and we have observed one fatal case. Clindamycin-induced colitis is presumably uncommon, and may occur more frequently when the drug is used in elderly patients, or when prolonged courses are given. When diarrhea occurs during the course of clindamycin therapy the drug should be stopped, and it seems advisable not to give antidiarrheal agents such as paregoric or diphenoxylate (Lomotil), since it is possible that such agents may potentiate the development of severe colitis. Because of the gastrointestinal side effects of oral lincomycin and clindamycin, erythromycin seems preferable as an oral penicillin-substitute in gram-positive cocal infections in the absence of specific indications for the other drugs.

The parenteral forms of lincomycin and clindamycin are much less irritating than is parenteral erythromycin, so that these drugs are preferable when intramuscular or intravenous therapy is indicated. When given intravenously, the drugs should be diluted and given by infusion over at least 30 minutes, since cardiorespiratory arrest has occurred when large doses are injected rapidly. Otherwise, parenteral lincomycin or clindamycin is quite well tolerated.

Lincomycin and clindamycin accumulate in bone and have been used very effectively in gram-positive osteomyelitis. Both drugs cross the blood-brain barrier poorly, even when the meninges are inflamed, so that they should not be used in central nervous system infections. Ultimately, the most important use of clindamycin may be in the treatment of *Bacteroides* infection, a topic considered elsewhere in this symposium.

### **Vancomycin**

Vancomycin is a rather toxic drug that is little used at present. It can cause serious ototoxicity and nephrotoxicity.<sup>26</sup> In addition, during administration of vancomycin, chills, fever and hypotension may develop. In spite of these disadvantages, vancomycin has potent bactericidal activity against most gram-positive cocci, and in certain unusual situations it can be quite useful. At present, the major example is enterococcal endocarditis in a patient highly allergic to penicillin. Vancomycin also is effective against most methicillin-resistant staphylococci.<sup>4</sup> As noted previously, these organisms are not yet a major problem in the United States, but they may well become so in the future.

### **AGENTS USED CHIEFLY FOR GRAM-NEGATIVE INFECTIONS**

There are a number of drugs used primarily in treating gram-negative infections which have activity against gram-positive cocci. Since

**Table 2.** *Reduction in Dosage of Antibiotics Required in Patients with Severe Renal Failure\**

	SERUM HALF-LIFE (HOURS)	
	Normal	Anuric or Oliguric
Group I—No reduction in dosage		
Erythromycin	1.5	5
Chloramphenicol	1.5-3	3-4
Doxycycline	15-20	15-20
Group II—Modest reduction in dosage		
Penicillin G	0.5	7-10
Ampicillin	0.8-1.8	6.5-18.2
Methicillin	0.5	4
Cephalothin	0.5-0.85	3 (early) 12-18 (late)
Cephalexin	0.6-1.2	18-30
Lincomycin	4.5	12
Group III—Marked reduction in dosage		
Streptomycin	2-3	52-110
Kanamycin	2-3	43-84
Gentamicin	2-3	55-67
Carbenicillin	1	15.7±5.2
Group IV—Avoid in renal failure		
Cephaloridine	1.5	20-23
Vancomycin**	6	200
Tetracycline	8.5	57-108

\*Modified from tables presented by Kunin<sup>15</sup> and by Wolinsky and Calia.<sup>31</sup>

\*\*In exceptional cases may be used if no effective alternative drug is available for treatment of life-threatening infection caused by susceptible organism; serial serum assays of vancomycin must be used for dosage adjustment.

these will be described in detail elsewhere in this symposium, the brief comments here will be limited to their possible role in gram-positive coccid infection.

The *tetracyclines* were introduced as "broad spectrum" antibiotics, and they indeed do have bacteriostatic activity against many gram-positive cocci. Resistance is a problem, however, not only with staphylococci but also with pneumococci and streptococci. The gram-negative activity of the tetracyclines is of no value in treating gram-positive infections, and it can cause problems by altering normal flora and encouraging superinfection. Because of the availability of better and more specific agents, tetracyclines rarely are indicated in infections known or suspected to be caused by gram-positive cocci.

*Chloramphenicol* also has activity against many gram-positive pathogens. Since it has no advantage over other drugs which are safer, it has no place in the therapy of the usual gram-positive infection. It is useful in the treatment of brain abscess and other central nervous system infections, since it crosses the blood-brain barrier well even in the absence of meningeal inflammation.

The *sulfonamides* at one time were widely used in the therapy of

**Table 3.** *An Approach to Therapy of Some Gram-Positive Coccid Infections<sup>1</sup>*

Streptococcal pharyngitis<sup>2</sup>

1. Benzathine penicillin G 1,200,000 units I.M.<sup>2</sup> *or*  
Potassium penicillin V 250-500 mg. p.o. q.i.d. × 10 days *or*  
Procaine penicillin G 600,000 units I.M. q.d. × 10 days
2. Erythromycin 500 mg. p.o. q.i.d. × 10 days<sup>3</sup>

Pneumococcal pneumonia, proven or suspected<sup>4</sup>

*Mild to moderate severity, normal host<sup>5</sup>*

1. Potassium penicillin V, 250-500 mg. p.o. q.i.d.
2. Erythromycin 500 mg. p.o. q.i.d.<sup>3</sup>

*Moderate to severe, normal host<sup>6</sup>*

1. Penicillin G 600,000 units I.V. q.6 h. until patient improving; then,  
potassium penicillin V 500 mg. p.o. q.6 h. *or*  
procaine penicillin G 600,000 units q.12 h.
2. Cephalothin 1 gm. I.V. q.4-6 h.<sup>3</sup>
3. Clindamycin 150-300 mg. I.V. q.6 h.<sup>3</sup>

*Abnormal host defenses—alcoholism, severe neutropenia, etc.<sup>6</sup>*

1. Penicillin G 1,200,000 units I.V. q.6 h.
2. Cephalothin 2 gm. I.V. q.4-6 h.<sup>3</sup>
3. Clindamycin 300-600 mg. I.V. q.6 h.<sup>3</sup>

Pneumococcal endocarditis<sup>7</sup>

1. Penicillin G 2,000,000 units I.V. q.4 h.
2. Cephalothin 2 gm. I.V. q.4 h.<sup>3</sup>
3. Clindamycin 600 mg. I.V. q.6 h.<sup>3</sup>

Pneumococcal meningitis<sup>8</sup>

1. Penicillin G 2,000,000 units I.V. q.2 h. *or*  
Ampicillin 1 gm. I.V. q.2 h.<sup>9</sup>
2. Cephaloridine 1 gm. I.M. *or* I.V. q.6 h.<sup>3, 10</sup>
3. Erythromycin 1 gm. I.V. q.4 h. for 3-4 days, then 1 gm. I.V. q.6 h.<sup>3</sup>

Staphylococcal pneumonia, proven or suspected<sup>11</sup>

1. Oxacillin<sup>12</sup> 2 gm. I.V. q.4-6 h. Change to penicillin G 1,000,000 units q.4 h.  
if staphylococcus proven sensitive to penicillin G.
2. Cephalothin 2 gm. I.V. q.4-6 h.<sup>3</sup>
3. Clindamycin 600 mg. I.V. q.6 h.<sup>3</sup>

Staphylococcal endocarditis<sup>13</sup>

1. Oxacillin<sup>12, 14</sup> 2 gm. I.V. q.4 h. Change to penicillin G 2,000,000 units q.4 h.  
if staphylococcus proven sensitive to penicillin G.
2. Cephalothin 2 gm. I.V. q.4 h.<sup>3</sup>
3. Clindamycin 600 mg. I.V. q.6 h.<sup>3</sup>

Staphylococcal meningitis<sup>15</sup>

1. Oxacillin<sup>12</sup> 2 gm. I.V. q.3 h. Change to penicillin G 2,000,000 units I.V. q.2 h.  
if staphylococcus proven sensitive to penicillin G.
2. Erythromycin 1 gm. I.V. q.4 h.<sup>3</sup>
3. Cephaloridine 1 gm. I.V. q.6 h.<sup>3, 16</sup>

Streptococcus viridans endocarditis<sup>7</sup>

1. Penicillin G 3,000,000 units I.V. q.4 h.
2. Cephalothin 2 gm. I.V. q.6 h.<sup>3</sup>
3. Clindamycin 300 mg. I.V. q.6 h.<sup>3</sup>

(Table continues on opposite page.)

**Table 3.** *An Approach to Therapy of Some Gram-Positive Coccal Infections<sup>1</sup> (Continued)***Enterococcal endocarditis<sup>7</sup>**

1. Penicillin G 3,000,000 units I.V. q.4 h. plus streptomycin 0.5 gm. I.M. q.12 h. or ampicillin 2 gm. I.V. q.4 h.
2. Erythromycin 1 gm. I.V. q.4 h. plus streptomycin 0.5 gm. I.M. q.12 h.<sup>2</sup>
3. Vancomycin 1 gm. I.V. q.12 h.<sup>3</sup>

<sup>1</sup>Doses cited are typical doses which might be used in average-sized adults. They should be changed appropriately for very large or very small adults and for children.

<sup>2</sup>Procaine penicillin G 600,000 units I.M. may be given in addition if symptoms are severe.

<sup>3</sup>Alternate therapy for patients allergic to penicillin.

<sup>4</sup>Treatment can be discontinued when patient has been afebrile for 48 to 72 hours and is improving clinically.

<sup>5</sup>Patients not admitted to the hospital.

<sup>6</sup>Patients treated in the hospital.

<sup>7</sup>Treatment should be continued for 4 weeks. Dose should be adjusted on basis of serum inhibition levels obtained after initial therapy begun.

<sup>8</sup>Treatment should be continued for at least 10 to 14 days. The patient should be free of signs and symptoms of meningitis for 3 to 5 days, and the cerebrospinal fluid should have a normal glucose and no more than 20 to 30 mononuclear cells.

<sup>9</sup>May be used as initial therapy if causative organism not clearly identified on gram stain, because of the possibility of *H. influenzae*.

<sup>10</sup>Cephalothin may *not* be substituted. Cephaloridine is contraindicated if renal function is reduced.

<sup>11</sup>Therapy should be continued 4 weeks. Oral dicloxacillin, 500 mg. q.4 h., may be substituted during the last 2 weeks.

<sup>12</sup>Nafcillin or methicillin may be substituted. Methicillin should be used in increased dosage, e.g., 3 gm. q.4 h.

<sup>13</sup>Therapy should be continued for 6 weeks.

<sup>14</sup>After patient has improved on I.V. therapy, oral dicloxacillin, 500 mg. q.4 h., may be substituted. The patient ordinarily should remain in the hospital, and the adequacy of serum inhibition levels should be checked periodically.

<sup>15</sup>Therapy ordinarily is continued for 4 weeks.

<sup>16</sup>This therapy should be effective, but there is little actual clinical experience with cephaloridine in staphylococcal meningitis.

gram-positive infections, but they have been superseded by more effective drugs.

The *aminoglycosides* are used chiefly in gram-negative infections, but certain of them have potentially useful activity against gram-positive cocci. *Gentamicin* is active against many gram-positive pathogens. In most instances it should not be used in gram-positive coccal infections, since effective and less toxic alternative agents are available. It can be used effectively against some strains of methicillin-resistant staphylococci.<sup>1</sup> The combination of cephalothin and *kanamycin* also has been reported to be effective against some methicillin-resistant staphylococci.<sup>1</sup> *Streptomycin* is useful as an adjunct to penicillin G or ampicillin in the treatment of enterococcal endocarditis.<sup>13, 24</sup>

## CONCLUSIONS AND RECOMMENDATIONS

Any attempt to formulate a comprehensive set of recommendations for the therapy of gram-positive coccal infections is fraught with dif-

ficulty. The great variations in severity of infection and in the characteristics of the host<sup>28</sup> impose a continuing requirement for clinical judgment in prescribing appropriate therapy for the individual patient. In particular, abnormalities of renal function often require modification of therapy (Table 2). The recommendations in Table 3 represent one necessarily arbitrary approach to the problem.

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## Antimicrobial Drugs for Treatment of Infections Caused by Aerobic Gram-Negative Bacilli

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In recent years, infection caused by aerobic gram-negative bacilli, especially members of the families Enterobacteriaceae and Pseudomonas, have become a major therapeutic problem. These infections frequently develop in pediatric, medical, or surgical patients who have limited ability to resist infection,<sup>2, 29, 30, 32, 34, 48, 61, 70</sup> and they are associated with considerable morbidity and mortality. The pathogenic bacilli have the unfortunate capacity to resist or circumvent the action of many antimicrobial agents. Antibiotics that are likely to be effective often have the greatest potential for producing serious or life-threatening side effects. The present report is concerned with certain antibacterial drugs which, when used discriminately and in accord with basic principles of effective antimicrobial therapy, may be effective for treatment of serious infections caused by aerobic gram-negative bacilli.

Table 1 lists the antimicrobial agents currently considered to be useful for treatment of serious infections produced by prevalent aerobic gram-negative bacilli. The physician should require that his hospital laboratory closely monitor the antimicrobial susceptibility patterns of gram-negative pathogens because these patterns may change with time and may vary from one hospital to another. Lorian<sup>56</sup> has recently discussed the mechanisms of action of antibiotics on gram-negative bacilli and has presented important information relevant to resistance and susceptibility.

### PENICILLINS

Two of the newer semisynthetic derivatives of benzylpenicillin, ampicillin (alpha-aminobenzylpenicillin) and carbenicillin (alpha-carboxy-phenyl penicillin), have broadened the range of antimicrobial activity of

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**Table 1.** *Clinically Useful Antimicrobial Drugs For Serious Infections Caused by Aerobic Gram-Negative Bacilli*

Ampicillin	Hemophilus influenzae; E. coli; Proteus (P) mirabilis; Salmonellae;* Shigella*
Carbenicillin	E. coli, P. mirabilis; indole-positive Proteus** Pseudomonas aeruginosa; some Enterobacter
Cephalosporins***	E. coli; Klebsiella, P. mirabilis
Chloramphenicol	E. coli; Klebsiella; P. mirabilis, Hemophilus influenzae, Salmonellae*
Gentamicin	E. coli; Klebsiella-Enterobacter-Serratia; P. mirabilis; indole-positive Proteus;* Pseudomonas aeruginosa
Kanamycin	E. coli;* Klebsiella*-Enterobacter-Serratia; P. mirabilis; indole-positive Proteus*
Polymyxins†	E. coli; Klebsiella-Enterobacter; Pseudomonas aeruginosa
Tetracyclines	E. coli
Trimethoprim-sulfamethoxazole	E. coli, Klebsiella, Enterobacter, P. mirabilis; indole-positive Proteus**

\*Resistant strains have emerged recently in some areas

P. morganii, P. rettgeri, P. vulgaris

†Cephalothin, cephaloridine, cephalexin, cefazolin, cephalixin

†Effective primarily for infections arising in urinary tract

penicillin to include a significant number of gram-negative pathogens. Both ampicillin and carbenicillin retain the minimal toxicity which characterizes penicillin and are thus often useful in patients who have underlying disease as well as gram-negative bacillary infection. For maximum efficacy, both drugs must be administered in sufficient dosage and usually parenterally rather than orally.

## Ampicillin

Ampicillin was originally considered as a drug of choice in salmonellosis, shigellosis, and infections due to *E. coli* or *P. mirabilis*,<sup>48</sup> but the incidence of resistant strains among these organisms has been increasing in the past several years.<sup>70, 91, 96</sup> A major factor in the emergence of this resistance has been the ability of gram-negative bacilli to utilize the episomal-mediated R-factor mechanism of multiple drug resistance. A contributing factor has been a widespread and often inappropriate over-use of this drug. An example of such over-use was recently pointed out by Ross et al. concerning ampicillin-resistant *Shigellae*.<sup>79</sup> In many areas, including the United States, ampicillin can no longer be designated as the drug of choice for *Shigellae*.<sup>47</sup> The majority of strains of *Klebsiella-Enterobacter-Serratia*, indole-positive *Proteus*, and *Pseudomonas aeruginosa* are resistant to ampicillin.

Ampicillin is useful in pertussis when it is administered in the catarrhal stage of the infection. Virtually all strains of *H. influenzae* are susceptible to ampicillin in vitro in concentrations less than 1 microgram per ml.,<sup>4</sup> and this drug is indicated in acute respiratory infections caused by *H. influenzae*.<sup>38</sup> There is conflicting opinion concerning the designation of ampicillin or chloramphenicol as the drug of choice in *H. influen-*

zae meningitis.<sup>4, 55, 83</sup> A more complete discussion of antimicrobial therapy for meningitis is presented elsewhere in this symposium. However, it should be emphasized that for treatment of meningitis, ampicillin must be given intravenously in maximal doses to avoid relapse.<sup>55</sup>

In neonatal sepsis caused by enteric gram-negative bacilli, a combination of ampicillin and kanamycin or gentamicin is currently recommended.<sup>24, 35, 38, 63</sup> Ampicillin has been used in the treatment of biliary tract infections caused by susceptible organisms since it is excreted in active form in the bile and undergoes enterohepatic circulation.<sup>94</sup> The serum half-life of ampicillin is increased in patients with impaired renal function. However, in patients with urinary infection and impaired renal function, therapeutic urinary concentrations of ampicillin may be achieved without toxicity when the creatinine clearance is greater than 10 ml. per minute.<sup>38</sup>

A major disadvantage of ampicillin is its pronounced tendency to produce severe skin rashes. The rash is usually maculopapular and may develop during or after treatment with the drug. This may occur in as many as 8 to 10 per cent of all patients. The incidence is considerably higher (60 to 100 per cent) in patients with infectious mononucleosis, possibly because of an interaction between the Epstein-Barr virus and ampicillin.<sup>45</sup> The rash occurs more often in females and is not related to age since it occurs with equal frequency in children and adults.<sup>5, 45</sup>

Lee and Hill reported an increased incidence (56 per cent) of rash, desquamation, fever, and immediate hypersensitivity reactions in patients with renal impairment who received 500 mg. every 6 hours.<sup>54</sup> Permanent deterioration of renal function occurred in a small number of these patients. No adverse reactions were observed in a second group of patients with poor renal function who received only 500 mg. of ampicillin per day.<sup>54</sup> The rash does not appear to represent a true penicillin allergy and its occurrence does not necessarily rule out further treatment with ampicillin or other penicillins.<sup>5, 45</sup> There is no significant increase of circulating antibody or positive skin test reactions to ampicillin or penicillin in children exhibiting ampicillin rash.<sup>45</sup>

An excess of ampicillin rashes has been noted in the presence of hyperuricemia and/or in conjunction with administration of allopurinol.<sup>10</sup> The frequent occurrence of diarrhea with oral ampicillin therapy has limited the use of this drug, particularly in pediatric patients; hetacillin, an ampicillin derivative, is reported to reduce this problem.<sup>3, 72</sup> Hetacillin possesses no antibacterial activity, but is hydrolyzed in the body to form active ampicillin. Hetacillin is more stable at acid pH. Serum levels accumulate more slowly and persist longer, although at a lower level than ampicillin. Any advantage of hetacillin over ampicillin is questionable and suggested doses may be inadequate.<sup>71, 91</sup>

In children, the recommended daily dosage of ampicillin is 50 to 200 mg. per kg., but in meningitis and other severe infections as much as 400 mg. per kg. in 4 to 6 equally divided doses have been used. The adult dose is 6 to 12 gm. per day, given parenterally in 4 to 6 doses. Intramuscular injection of 0.5 to 1 gm. of ampicillin achieves peak serum levels of 7 and 10 micrograms per ml., respectively, and the drug is present in serum for 6 hours.<sup>94</sup>

## Carbenicillin

Carbenicillin has activity comparable to ampicillin against *P. mirabilis* and *E. coli*, but is unique among penicillins for its activity against *P. aeruginosa* and indole-positive strains of *Proteus*. *Klebsiellae*, *Serratia*, and the majority of strains of *Enterobacter* are notably resistant.<sup>10</sup> Carbenicillin has been particularly effective in the treatment of gram-negative bacillary infections in patients with malignancy and neutropenia.<sup>9</sup> Emergence of resistance is thought to be a principal problem with carbenicillin;<sup>10</sup> however, this has been less of a problem in the United States<sup>71</sup> and may result from variations of in vitro antimicrobial susceptibility testing.

Mean serum carbenicillin concentrations following a 1 gm. intramuscular dose are 18 micrograms per ml. at 1 hour, 14 micrograms per ml. at 3 hours, and 6 micrograms per ml. at 6 hours. These concentrations are sufficient to inhibit *E. coli* and most *Proteus* species, but are inadequate for almost all strains of *Pseudomonas aeruginosa*.

Intravenous infusions of carbenicillin (5 gm. over 2 hours) result in peak serum levels of 200 micrograms per ml., which are sufficient to inhibit all but the most resistant *Pseudomonas* species.<sup>10</sup> Probenecid delays renal excretion and helps to maintain therapeutic serum concentrations over a longer interval. Renal and non-renal clearance of carbenicillin is considerably less than that of other penicillins.<sup>88</sup>

During the 2 years we evaluated the efficacy and tolerance of carbenicillin in patients with cystic fibrosis, almost 45 per cent of the *Pseudomonas* strains became resistant by disk susceptibility, either during or subsequent to a 2 week course of therapy.<sup>11</sup> In view of the possibility of emergence of resistance, the use of carbenicillin should be restricted to patients with serious infections produced by *Pseudomonas aeruginosa*, indole-positive *Proteus*, and susceptible strains of *Enterobacter*. Patients receiving carbenicillin must be closely monitored for superinfection. Greater efficacy and a delay in the emergence of resistance results when patients are treated with large doses of carbenicillin or in combination with gentamicin.<sup>11, 25, 40, 46, 86</sup>

It should be noted that inactivation of gentamicin by carbenicillin has been reported.<sup>60</sup> This occurs only after prolonged in vitro incubation with high concentrations of carbenicillin and is theoretically possible in vivo only in patients with renal failure. Mixing the two drugs in the same solution for parenteral administration is contraindicated, but each may be given separately.

Transient serum glutamic oxalacetic acid transaminase (SGOT) elevations without apparent liver damage have been noted in patients receiving carbenicillin.<sup>12</sup> Carbenicillin is a di-sodium salt and each gram contains 108 mg. (4.7 mEq.) of sodium; since large daily doses (300 to 500 mg. per kg. in children or 20 to 30 gm. in adults) are usually administered, careful surveillance of the patient's electrolyte and cardiac status is mandatory.<sup>11</sup> Poorly characterized minor bleeding disorders have been associated with carbenicillin usage, and as with other penicillins, seizures or neuromuscular irritability can occur in the presence of unusually elevated serum levels. Dose-related reversible granulocytopenia has been reported.<sup>76</sup>

Carbenicillin in the form of alpha-carboxybenzylpenicillin is poorly absorbed from the gastrointestinal tract.<sup>14</sup> A 5-indanyl ester of carbenicillin, indanyl carbenicillin, is now commercially available.<sup>15</sup> Although relatively stable at acid pH and absorbed from the intestine, indanyl carbenicillin yields low blood levels and should not be used for the treatment of systemic infections. Antibacterial levels attained in the urine are sufficient to inhibit many strains of *E. coli*, *Proteus*, *Pseudomonas*, and some *Enterobacter*. Thus far, it compares favorably with ampicillin and oral cephalosporins in the treatment of urinary tract infections, but as with its parent antimicrobial, it should be reserved for urinary tract infections due to *Pseudomonas*, indole-positive *Proteus*, and sensitive strains of *Enterobacter*.<sup>77</sup> Recommended dosage is 50 to 100 mg. per kg. daily in equally divided oral doses administered every 6 hours. Adults should receive 0.5 to 1.0 gm. orally every 6 hours. The presently available oral preparation has an extremely disagreeable taste and may cause vomiting and diarrhea.<sup>92</sup>

## CEPHALOSPORINS

The cephalosporin group of antimicrobials is similar in structure to the penicillins. The structural nucleus of this group of agents is 7-aminocephalosporanic acid which resembles 6-aminopenicillanic acid, the structural nucleus of the penicillins. In spite of this structural similarity and the fact that they have the same mechanism of action on the bacterial cell wall as the penicillins, penicillinase does not inactivate the cephalosporins. They are hydrolyzed by another beta-lactamase, cephalosporinase, which is produced by certain gram-negative bacteria, principally *Pseudomonas*, *Enterobacter*, indole-positive *Proteus*, and *Serratia* which are resistant to the cephalosporins. *Klebsiellae*, *E. coli* and *P. mirabilis* are usually susceptible to the cephalosporins.<sup>6</sup>

Cephalothin and cephaloridine are poorly absorbed from the gastrointestinal tract and must be administered parenterally. Cephalothin is quite irritating and painful when injected by either parenteral route but is not nephrotoxic. Cephaloridine is relatively painless when given parenterally but causes renal tubular damage with excessive dosage. Blood levels achieved with cephaloridine are higher and more prolonged than with cephalothin because of greater stability and a lower renal clearance.<sup>6</sup> Renal impairment is a contraindication to the use of cephaloridine, except possibly in anephric patients on chronic dialysis.<sup>73</sup> Both cephalothin and cephaloridine should be reserved for treatment of serious infections. Cefazolin, a newly released semisynthetic parenteral cephalosporin has a similar spectrum of antibacterial activity but achieves higher and more prolonged blood levels with comparable doses. Nephrotoxicity has not yet been observed and the drug is well tolerated after parenteral injection.<sup>16</sup> The dosage of cephalothin and cefazolin should be reduced in patients with impaired renal function.

Cephaloglycin and cephalixin are the two cephalosporin preparations currently available for oral administration and are useful primarily for urinary tract infections. Superiority of one drug over the other has not

been established but cephalixin gives good blood and tissue as well as urine levels.<sup>7</sup> Patients with chronic renal bacteriuria reportedly respond poorly to treatment with cephaloglycin.<sup>71</sup>

Cephalosporins produce certain adverse reactions which may be particularly important to recognize in the compromised host. False-positive direct Coombs reactions may occur, particularly when large doses of cephalothin are administered to patients with poor renal function. A cephalothin-globulin complex coats the erythrocytes and agglutination occurs with anti-human globulin serum which may interfere with cross-matching of blood. False-positive direct Coombs tests may also occur with other cephalosporins but hemolytic anemia is seldom a consequence of this phenomenon.<sup>6</sup>

When testing urine of patients on cephalosporins with Clinitest tablets or Benedict's or Fehling's solution, a dark discoloration may develop and be mistaken for a positive reaction for glucose. Specific tests utilizing glucose oxidase (Dextrostix or Testape) are not associated with this reaction.

Cephalosporins should be used cautiously in patients who are allergic to penicillins.

Cephalothin may be administered to children in a daily dosage of 40 to 80 mg. per kg. divided into 4 equal doses. The usual adult dose is 6 to 12 gm. daily, administered parenterally in equally divided doses at 4 to 6 hour intervals. In children, cephaloridine may be administered in a dosage of 30 to 50 mg. per kg. daily, doubling the dose cautiously in the presence of severe infections. Adult dosage is 0.5 to 1 gm. every 6 to 8 hours; total daily dosage should not exceed 4 gm. Renal function must be carefully monitored in all patients receiving cephaloridine, because nephrotoxicity may occur even with recommended doses. Initial dosage recommendations for cefazolin therapy for gram-negative bacillary infection resemble those for cephaloridine.

## AMINOGLYCOSIDES

Streptomycin, neomycin, kanamycin, and gentamicin are the commercially available aminoglycoside antibiotics which have been used for parenteral therapy of serious infections caused by aerobic gram-negative bacilli. Tobramycin, BB-K8, sisomycin and butirosin are new aminoglycoside antibiotics which are currently undergoing investigation. Presently there appears to be little indication for use of streptomycin or neomycin for treatment of systemic infections caused by gram-negative bacilli. Most of those organisms are now resistant to streptomycin,<sup>81</sup> and parenteral neomycin appears to be considerably more toxic than kanamycin or gentamicin.<sup>74, 84, 95</sup>

### Kanamycin

Kanamycin is effective against a majority of strains of *E. coli*, *Klebsiella-Enterobacter-Serratia*, and *Proteus*. It may also be effective against some strains of opportunistic bacilli such as *Mima-Herellea* and *Flavobacterium*, but is ineffective against the majority of strains of *Pseudomonas aeruginosa* and *Bacteroides*. In recent years, there have

been disturbing reports of an increasing incidence of strains of *E. coli* and *Klebsiella* resistant to kanamycin.<sup>1, 63</sup> For example, McCracken reported that the percentage of kanamycin-resistant strains of *E. coli* isolated from the blood of infants at the Parkland Memorial Hospital in Dallas, Texas, increased from approximately 5 per cent in 1963 to 1967 to 25 to 30 per cent from 1968 to 1970.<sup>63</sup>

The most serious toxic effects of kanamycin are ototoxicity, nephrotoxicity and, rarely, respiratory arrest.<sup>71</sup> These adverse effects will be considered in more detail in another paper in this symposium.<sup>93</sup> Kanamycin is poorly absorbed from the gastrointestinal tract and requires parenteral administration for treatment of systemic infections. Occasionally therapeutic or toxic levels of kanamycin (and neomycin) have been achieved in the blood after repeated oral administration of the drug to patients with impaired renal function.<sup>49, 52</sup> Kanamycin is not appreciably bound to serum protein<sup>33</sup> and diffuses well into most tissues and biologic fluids. However, the antibiotic diffuses poorly into bile, feces, amniotic and prostatic fluids, and into the noninflamed meninges.<sup>23, 50, 95</sup>

Kanamycin has been effective for treatment of infections caused by aerobic gram-negative bacilli resistant to less toxic alternative agents. Some of the more serious bacillary infections that have responded to kanamycin (either alone or in combination with other drugs) are septicemia, endocarditis, pneumonia, peritonitis, acute pyelonephritis, and septic endometritis. Intramuscular kanamycin is recommended and routinely employed in the treatment of neonatal meningitis; however, in some patients susceptible strains of gram-negative bacilli have not been eradicated from the cerebrospinal fluid.<sup>66</sup> It remains to be determined whether or not intramuscular administration of kanamycin produces adequate cerebrospinal fluid levels of the drug in neonates with meningitis.<sup>66</sup>

The usual dosage of kanamycin for serious infections is 15 mg. per kg. of body weight daily, administered intramuscularly in two equally divided doses at 12 hour intervals. The maximum daily dose should not exceed 1.5 gm. and duration of therapy should not be unnecessarily prolonged;<sup>27</sup> the status of renal and auditory function should be monitored carefully. For premature infants less than 3 weeks of age, a kanamycin dosage of 7.5 mg. per kg. intramuscularly every 12 hr. should not be exceeded, and 5 mg. per kg. intramuscularly every 12 hr. may be a safer but still effective schedule.<sup>85</sup>

Since kanamycin is excreted primarily by glomerular filtration, toxic concentrations of the drug may accumulate in the body if dosage is not adjusted for patients with impaired renal function. Cutler and Orme<sup>21</sup> recently pointed out that the serum creatinine concentration provides a basis for adjustment of dosage of kanamycin in patients with chronically impaired renal function. They found that the serum half-life of kanamycin (in hours) could be estimated by multiplying the value of the serum creatinine concentration (mg. per 100 ml.) by 3. The recommended dosage interval for kanamycin was every third half-life or approximately 9 times the value of the serum creatinine concentration in patients with stable impairment of renal function. McCloskey and Becker<sup>62</sup> subsequently confirmed the clinical usefulness of this method.

## Gentamicin

Gentamicin is a bactericidal aminoglycoside antibiotic that has an unusually wide spectrum of activity against aerobic gram-negative bacilli. It is effective against a majority of strains of *E. coli*, *Klebsiella-Enterobacter-Serratia*, *Proteus mirabilis*, indole-positive *Proteus*, and *Pseudomonas aeruginosa*.<sup>43, 47, 65, 81</sup> but is ineffective against most strains of anaerobic gram-negative bacilli (*Bacteroides*).<sup>28</sup> It appears to be effective against strains of aerobic gram-negative bacilli which have acquired resistance to kanamycin.<sup>39, 43, 47</sup> The vast majority of gram-negative bacilli shown to be susceptible to gentamicin will be inhibited by 5 micrograms per ml. or less of the drug. Gentamicin is considerably more active in vitro in an alkaline medium than in an acid medium.<sup>43</sup> Increased concentrations of calcium or magnesium ions in the culture media significantly increase the minimum concentrations of gentamicin required for inhibition of growth of *Pseudomonas aeruginosa*.<sup>31</sup>

Gentamicin is a very stable compound—it does not deteriorate on storage, will survive freezing and boiling, and will withstand autoclaving for 20 minutes. It is potentially ototoxic and nephrotoxic;<sup>26</sup> rarely, it has caused respiratory arrest. It appears to be more likely to cause vestibular toxicity than deafness.

Gentamicin is poorly absorbed from the gastrointestinal tract and requires parenteral administration. It is rapidly absorbed after intramuscular administration,<sup>8</sup> is not appreciably bound to serum proteins,<sup>33</sup> and is distributed in about 15 per cent of the body weight.<sup>43</sup> Gentamicin does not achieve high concentrations in bile or in the cerebrospinal fluid when the meninges are not inflamed.

Black and his associates<sup>8</sup> found that the peak blood level of gentamicin in micrograms per milliliter (after a single intramuscular injection in adults with normal renal function) was approximately 4 to 6 times the administered dose in milligrams per kilogram of body weight. Other investigators found considerable variations in the dose-response curves of gentamicin in patients with normal renal function when intramuscular dosage was based upon the weight of the patient.<sup>42</sup>

In adults, approximately 10 per cent of gentamicin appears to be bound to red blood cells, and anemic patients may have higher serum concentrations of the drug than patients with normal red cell volume.<sup>75</sup> However, in infants under 2 weeks of age there appears to be no correlation between peak concentrations of gentamicin in the serum and values of hemoglobin and hematocrit.<sup>64</sup>

The recommended dosage of gentamicin for serious infections of newborn infants is 5 to 7.5 mg. per kg. daily, administered intramuscularly or intravenously in 2 or 3 equally divided doses.<sup>64</sup> For adults with normal renal function, the usual dosage is 3 to 5 mg. per kg. daily, administered intramuscularly or intravenously in 3 equally divided doses at 8 hour intervals.

Since gentamicin is not metabolized and is excreted primarily by glomerular filtration, toxic concentrations of the drug may accumulate in the body when dosage is not adjusted for patients with impaired renal function.<sup>36</sup> McHenry et al.<sup>67</sup> showed that in patients with various degrees of impaired renal function there was a linear relationship between

the per cent hourly loss of gentamicin and the endogenous creatinine clearance. The per cent hourly loss could be estimated by dividing the value of the endogenous creatinine clearance (ml. per min. per 1.73 m.<sup>2</sup>) by 4. Also there was a significant relationship between the serum creatinine concentration and the serum half-life of gentamicin.<sup>67</sup> The half-life of gentamicin (in hours) could be estimated by multiplying the value of the serum creatinine concentration (mg. per 100 ml.) by 4; this was confirmed by Cutler and associates.<sup>20</sup> These data provide a possible basis for individualized adjustment of dosage of gentamicin in patients with chronically impaired renal function. However, it may be necessary to utilize serial assays of serum gentamicin levels as a guide to dosage in patients with rapidly changing renal function or in those in whom infection does not appear to be responding to therapy. Rapid methods for assay of gentamicin have recently been described.<sup>58, 80, 87</sup>

Gentamicin appears to be effective for treatment of aerobic gram-negative bacillary infections of the urinary tract,<sup>17</sup> lungs,<sup>57</sup> and burn wounds.<sup>89</sup> It has been used for treatment of serious postoperative wound infections, peritonitis, salpingitis, and osteomyelitis.<sup>18</sup> Gentamicin does not reach high concentrations in bile, and failure of gentamicin therapy has been reported in patients with cholangitis.<sup>43, 68</sup> Gentamicin has been useful in the control of chronic *Pseudomonas* pulmonary infection in patients with cystic fibrosis<sup>13</sup> even though high sputum levels and eradication of organisms have not occurred.<sup>59</sup>

Because of its broad range of antimicrobial activity and efficacy, gentamicin now appears to be the drug of choice for the initial presumptive therapy of bacteremia caused by aerobic gram-negative bacilli.<sup>60</sup> It must be emphasized, however, that neutropenic patients or those with leukemia may have persistent bacteremia despite concentrations of gentamicin in the blood that are effective in other patients. This may be due to a decreased number or diminished bactericidal capacity of circulating phagocytes.<sup>42</sup> Addition of carbenicillin to gentamicin may improve the outlook of treatment of *Pseudomonas* septicemia in granulocytopenic patients.<sup>9, 46</sup> Gentamicin does not appear to be effective for treatment of bacteremia in patients who have septic endovascular lesions.<sup>68</sup>

In those newborn nurseries in which kanamycin-resistant gram-negative bacilli have emerged, gentamicin in combination with ampicillin appears to be effective therapy for neonatal sepsis or meningitis.<sup>38</sup> However, parenteral administration of gentamicin may result in low concentrations of the drug in the spinal fluid and it may be necessary to supplement therapy with intrathecal or intraventricular injections of the drug in order to cure gram-negative bacillary meningitis in neonates or adults.<sup>64, 75</sup>

Some strains of *Pseudomonas aeruginosa* that are resistant to gentamicin may be susceptible to the newer aminoglycosides such as tobramycin, BB-K8, and butirosin. There is some evidence from animal studies that tobramycin may be slightly less toxic than gentamicin. Currently tobramycin is undergoing clinical investigation in a number of medical centers. In our hospital, tobramycin appears to be well tolerated and thus far 90 per cent of the *Pseudomonas* strains isolated from patients with cystic fibrosis have minimum inhibitory concentrations of 2.5

micrograms of tobramycin per ml. or less. However, resistance of these organisms appears to emerge more rapidly than it does with gentamicin.

## POLYMYXINS

The polymyxins are a group of basic polypeptides which are active against *Pseudomonas*, *E. coli*, *Enterobacter*, and *Klebsiella*, but usually inactive against *Proteus* or *Serratia*.<sup>11</sup> Polymyxin B and colistin (polymyxin E) are the preparations available for clinical use. The most serious toxic effects of these drugs are apnea, nephrotoxicity and cerebellar ataxia.<sup>13a</sup>

Polymyxins are not absorbed from the gastrointestinal tract and require parenteral administration. They diffuse poorly into tissues other than the urinary tract. Since polymyxins are excreted primarily by the kidneys, toxic concentrations of the drugs may accumulate in the body if dosage is not adjusted for patients with impaired renal function. Dosage recommendations are available for colistin,<sup>32a</sup> but there appear to be insufficient data to establish such guidelines for dosage of polymyxin B.

Polymyxin B and colistin appear to be effective for treatment of urinary infections caused by susceptible organisms,<sup>19, 38</sup> particularly in patients with normal renal function. Proof of efficacy of polymyxins for treatment of extrarenal infections appears to be lacking.<sup>22, 38</sup>

## MISCELLANEOUS ANTIMICROBIAL DRUGS

*Chloramphenicol* is active in vitro against many gram-negative bacilli and effective clinically since it diffuses widely into tissues.<sup>9a</sup> It is the drug of choice in the treatment of infections caused by *Salmonella typhi*,<sup>38, 41</sup> although resistant organisms have been reported.<sup>54</sup> The inability of premature and newborn infants to metabolize or excrete chloramphenicol normally and its hematopoietic toxicity in children and adults have limited its use. It may be administered orally or intravenously, but it is important to remember that the available sodium succinate preparation is not adequately absorbed and is therefore ineffective when administered intramuscularly.<sup>95</sup>

*Tetracyclines* are no longer considered primary drugs for treatment of systemic infections caused by aerobic gram-negative bacilli. Doxycycline, synthesized from oxytetracycline, and minocycline, a derivative of tetracycline, are two new tetracyclines available for oral and parenteral use; both offer only minimal advantages over tetracycline hydrochloride. They are stable at room temperature and do not break down to cause the pseudo-Fanconi syndrome produced by the use of outdated tetracyclines. Doxycycline does not accumulate in a patient with renal impairment. Food or milk does not interfere with absorption of these newer tetracyclines and they have longer serum half-lives.<sup>71</sup> Adverse effects such as hepatic toxicity, particularly in pregnancy, teeth staining in children, bone growth arrest in premature infants, and propensity to cause bacterial overgrowth and superinfection should be borne in mind.<sup>38, 51</sup>

*Sulfonamides* are useful primarily for urinary tract infections due to susceptible gram-negative bacilli and are seldom indicated for serious or systemic infections. Sulfamethoxazole-trimethoprim combination has recently been released in this country for use in chronic urinary tract infections, although it has been used abroad for systemic infections as well. Although not approved for such use in this country, this combination is considered suitable therapy for patients with typhoid fever resistant to both chloramphenicol and ampicillin.<sup>82</sup>

*E. coli*, *Klebsiella*, *Enterobacter* and *Proteus* are the gram-negative bacilli usually susceptible to this combination. Although trimethoprim is an inhibitor of dihydrofolic reductase and, as such, functions as a folate antagonist, well documented serious hematologic reactions are thus far few. Nephrotoxicity in patients with diminished renal function has been observed and may limit the usefulness of this combination therapy in patients with chronic urinary infections who may already have loss of renal function. The exact role of sulfamethoxazole-trimethoprim in managing urinary infections remains to be defined, but considerations of cost currently make sulfonamides alone, ampicillin or a tetracycline preferable choices when the infecting organisms are susceptible.<sup>90</sup>

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## Antimicrobial Considerations in Anaerobic Infections

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In some reviews antimicrobials are classified according to their ability to inhibit either gram-positive or gram-negative bacteria, a grouping which is far from satisfactory for these agents, but nonetheless widely employed. This distinction loses further validity when considering the large and diverse group of bacteria involved in anaerobic infections. Until quite recently, for most physicians this category was represented by tetanus, botulism, and gas gangrene, all caused by the spore-forming clostridia. Recently improved and simplified methods for recovering anaerobic organisms from clinical specimens, coupled with emphasis on prompt and proper handling and transport of specimens,<sup>37</sup> have promoted a far greater appreciation on the part of the medical profession for the extensive involvement of anaerobes in a wide array of common clinical conditions, as outlined in Table 1. As noted, in many situations, anaerobes are the causal agents or routinely participate with other organisms in a significant, but ill-defined and perhaps synergistic<sup>1, 2, 7, 29</sup> role, but also occur not infrequently in situations where other organisms are traditionally more frequently implicated. (See references 1, 2, 5, 7, 9, 13, 14, 18, 19, 26, 31, 36, 39, 43, 57, 58.) Zabransky recovered anaerobic species from almost 40 per cent of all bacteriologically positive specimens, representing one quarter of all the clinical specimens examined in a 6 month period at the Mayo Clinic.<sup>55</sup>

Even the small clinical laboratory is now equipped to isolate and characterize most of the clinically important anaerobes into broad categories. The true incidence of anaerobic participation in many clinical conditions is yet to be determined by more widespread application of these technical advances.<sup>48</sup> For example, the true incidence of anaerobic etiology in infective endocarditis is probably not known.<sup>9, 33</sup> Previous reports of a high proportion of "sterile" cultures from patients with brain and liver abscesses have yielded to more thorough studies documenting the pre-eminent role of anaerobic pathogens in these not uncommon infections.<sup>18, 26, 29, 39</sup>

Anaerobes comprise the major portion of man's indigenous micro-

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**Table 1.** *Infections in Which Anaerobes (Causal or Participatory) Should Routinely Be Anticipated or Where They May Be Recovered (in Parentheses) Under Appropriate Circumstances\**

**CEPHALIC**

*Intracranial:* brain abscess, otogenic meningitis, extradural or subdural empyema, chronic sinusitis, chronic otitis media

*Oral, dental, pharyngeal:* gingivitis, stomatitis or Vincent's angina, Ludwig's phlegmon, actinomycosis, root canal infection, dental abscess or sinus, peritonsillar abscess

**PLEUROPULMONARY**

Aspiration pneumonia, thoracic empyema, lung abscess, pneumonia secondary to obstruction, actinomycosis, bronchiectasis

**INTRA-ABDOMINAL, PELVIC**

Liver abscess, pyelphlebitis, subphrenic and other intra-abdominal abscesses, peritonitis, appendicitis, diverticulitis, wound infections following bowel surgery or abdominal trauma, blind-loop syndrome, actinomycosis, perirectal abscess, post-abortion and puerperal sepsis, endometritis, pelvic abscess and/or thrombophlebitis secondary to gynecologic surgery, tubo-ovarian abscess, Bartholin's abscess (prostatic abscess, prostatitis, pyelonephritis, pyonephrosis and other urinary tract infections, balanoposthitis)

**CUTANEOUS AND MUSCULOSKELETAL**

Gas gangrene or anaerobic myonecrosis, gas-forming cellulitis, infected pilonidal sinus, infected human and animal bites, progressive synergistic gangrene, breast abscess, infected diabetic or vascular gangrene (septic arthritis, osteomyelitis, necrotizing fasciitis)

\*Excluding tetanus and botulism which are specific intoxications.

flora and are present on the skin and all the mucous membrane surfaces of the body. The anaerobic gram-negative bacilli, especially bacteroides, are the most frequently recovered clinical isolates and normally reside as saprophytic commensals in the nose, mouth, nasopharynx, and lower intestinal and genitourinary tracts.<sup>15, 29</sup> In the colon, bacteroides outnumber the aerobic gram-negative bacilli by as much as 1000 to 1. Thus anaerobes represent a likely source of infection when tissue anoxia, necrosis, and vascular compromise lead to a break in the body's defenses.<sup>29</sup> Malignancy, bronchial and visceral obstructions, surgery, antecedent aerobic infection, antibiotic therapies (particularly preoperative bowel "sterilization" with nonabsorbable antibiotics such as kanamycin and neomycin), corticosteroid therapy, immunosuppressive and antineoplastic therapies, burns, and diabetes set the stage for these harmless saprophytes to become invasive pathogens responsible for a somewhat unique type of infectious process.<sup>7, 12, 29, 41</sup>

Why the overdue recognition for such a vast array of common clinical conditions? Although the anaerobic field has been championed for many years by a relatively small number of persistent investigators,<sup>1, 2, 13, 16, 18, 42, 52</sup> technical problems and a lack of clinical awareness have deceived most of the remaining profession from a full appreciation of the problem.

Specimens containing anaerobes are usually mixed with aerobes and facultative organisms as well. Since oxygen kills or suppresses most anaerobes, and since they grow more slowly than their companions, improper culture techniques easily result in their being overlooked. The use

of fluid media, such as thioglycollate or chopped meat broths, may mask the polymicrobial nature of these infections, which is best demonstrated by streaking specimens on properly incubated solid media.<sup>7</sup> If the specimen is not protected from oxygen during transport and is not cultured promptly on appropriate media, the more rapidly growing aerobes prevail, or the specimen is prematurely discarded when no growth appears or a single organism is recovered.

Although these technical considerations account for a large proportion of past oversights in this field, even more critical was the physician's failure to request anaerobic cultures, or to perform a gram stain, especially when this simple maneuver might alert him to the possibility of anaerobic involvement in settings laden with important clinical clues—foul or putrid odor or discharge, infection adjacent to a mucosal surface, necrotic tissue, gas in tissues or discharge, septic thrombophlebitis, icteric bacteremia, and especially gram-negative bacillary infections not responding to aminoglycoside or polymyxin.<sup>11, 13, 15</sup> Most important of all the missed clues is the gram stain with a mixture of gram-negative and gram-positive bacteria with no growth or but a single organism on the accompanying aerobic culture. One need not be expert in the morphology of anaerobes to profit from this simple examination and proceed accordingly.

Acknowledging the importance of anaerobes in such an array of infectious problems demands a certain degree of familiarity with their classification and nomenclature (Table 2). Although exact speciation is presently difficult for the average clinical laboratory and microbiologists themselves remain undecided on the classification of certain organisms, taxonomy in this hitherto forbidding area has been standardized to a certain extent.<sup>12</sup> Since anaerobes are frequently slower

**Table 2.** *Classification of Representative Anaerobic Pathogens\**

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Gram-negative bacilli

Bacteroides

*B. fragilis*, *B. oralis*, *B. melaninogenicus*

Fusobacterium (some formerly Sphaerophorus)

*F. nucleatum*, *F. varium*, *F. necrophorum*

Spore-forming gram-positive rods

Clostridium

*C. perfringens (welchii)*, *C. tetani*, *C. botulinum*, *C. novyi*,

*C. septicum*, *C. ramosum*

Non-sporeforming gram-positive rods

Actinomyces, Eubacterium, Bifidobacterium,

Propionibacterium, Catenabacterium

Anaerobic cocci

Gram-positive Peptococcus, Peptostreptococcus, microaerophilic streptococci and cocci

Gram-negative Veillonella

Miscellaneous

Treponemes (spirochetes)

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\*Not intended to be a complete list.

growing and more fastidious in their growth requirements than most aerobes, and since they appear most often in mixed cultures, specific identification is time-consuming, while individual strains are being isolated and studied. Likewise, rapid determination of antibiotic susceptibility may be delayed. More widespread use of selective media and other technical advances will undoubtedly circumvent these current obstacles,<sup>11, 17, 51</sup> but for the moment the physician is compelled to initiate therapy in an appropriate clinical setting on a presumptive basis, utilizing a high index of suspicion (Table 1) and, hopefully, a suspicious and characteristic gram stain.

## IN VITRO SUSCEPTIBILITY TESTING OF ANAEROBES

Since anaerobes grow more slowly than aerobes or facultative organisms, standardized (Kirby-Bauer-Sherris<sup>4</sup>) antibiotic paper disc susceptibility testing, which depends on growth achieved by overnight incubation, cannot be applied to the anaerobes without certain modifications, currently in progress.<sup>45, 46, 52, 54</sup> Agar and broth dilution studies are time-consuming and too demanding for routine clinical use. However, they have provided us with predictable susceptibility patterns which, for the moment, allow appropriate selection of antibiotics on a presumptive basis in most instances.<sup>11</sup> Consequently most of the data in this paper derive from these *in vitro* studies. Despite certain differences among investigating groups, reliable minimum inhibitory concentration and minimum bactericidal concentration patterns have emerged. Substantial progress has also been made toward defining more rapid and reliable paper disc susceptibility testing methods.

It should be emphasized that antimicrobial susceptibility testing of anaerobes differs in certain respects from the testing of aerobes. For example, the presence of increased concentrations of carbon dioxide, as generated in the current and widely used Gas Pak (BBL) jars, raises MICs for erythromycin and lincomycin on the order of 4- to 32-fold, either by lowering the pH of the agar or possibly by providing a more adequate inoculum for organisms with a carbon dioxide growth requirement.<sup>20, 21</sup> Agar pH changes have also been noted to alter the size of inhibitory zones around aminoglycoside discs.<sup>48</sup> Anaerobiosis alters results of susceptibility tests with certain penicillins.<sup>31, 35</sup> Humidity, initial and subsequent pH of the agar, blood, and other media components, the age of the culture and the size of the inoculum all must be thoroughly investigated before these methods are truly standardized.<sup>48</sup> The effect of anaerobiosis *per se* on the metabolism and lag phase of the organism's growth cycle, or indeed, possible alterations in the mechanism of antibiotic action in an anaerobic atmosphere, must be determined.<sup>38, 51</sup> Although rather uniform susceptibility patterns are currently available, continuous monitoring is necessary to anticipate changes in these sensitivity patterns, particularly with widespread usage of the more effective agents.

## THERAPEUTIC PRINCIPLES OF MANAGING ANAEROBIC INFECTION

In many instances, it is difficult if not impossible to assess the role of a single antibiotic in the management of a patient with an anaerobic infection. The polymicrobial nature of these infections usually requires the use of combinations of drugs to attack the aerobic pathogens as well, while the attendant tissue necrosis so characteristic of these disorders introduces a number of variables in evaluating any therapeutic response.

Surgical therapy is of paramount concern.<sup>1, 13, 29</sup> Thorough drainage of abscesses, debridement of necrotic tissues, and relief of obstruction are usually critical to the patient's recovery. Repeated surgical attack is quite the rule; the often concomitant septic thrombophlebitis contributes to a pronounced tendency for relapse and the need for high dose antibiotic therapy over a prolonged period.<sup>13</sup> Other therapeutic measures, such as antitoxins, hyperbaric oxygen, and the use of local oxygen or oxidizing agents are beyond the scope of this review, but may also benefit selected patients.<sup>29</sup> Antibiotic therapy, although vitally important, especially in terms of early exhibition, is but a single aspect of a complicated therapeutic problem.

### ANTIBIOTICS OF FIRST CHOICE

The recovery or anticipation of *Bacteroides fragilis*, a normal inhabitant of the gastrointestinal tract, the most frequently isolated clinically important anaerobic pathogen, and the most commonly isolated of all bacteroides species,<sup>5, 20, 25</sup> is the key to selecting either chloramphenicol or clindamycin, the two most broadly active of the currently approved antibiotics. In contrast to their action against most of the other bacteroides species, particularly those derived from the oral cavity, the penicillins are relatively ineffective.<sup>6, 7, 25, 30, 46</sup> *B. fragilis* is not uncommonly recovered from patients with anaerobic pleuropulmonary infections despite the greater frequency of penicillin-sensitive bacteroides in the oral cavity.<sup>2</sup>

Chloramphenicol, when tested by agar plate dilutions, or in thioglycollate broth,<sup>56</sup> is bacteriostatic for 100 per cent of *B. fragilis* strains, at therapeutically attainable concentrations of 3.1 to 12.5 micrograms per ml. in most studies,<sup>30, 32, 46</sup> although a few strains are more resistant in other laboratories;<sup>25, 56</sup> it is poorly bactericidal.<sup>32, 56</sup> Clindamycin inhibits 90 to 100 per cent of *B. fragilis* strains at a concentration of 3.1 micrograms and the remainder at 6.2 micrograms per ml. in agar dilution studies from a number of laboratories;<sup>25, 30, 32, 46</sup> bactericidal activity is erratic.<sup>32, 56</sup> The antibiotic paper disc diffusion technique is reliably predictive when testing *B. fragilis* against chloramphenicol, but with clindamycin results have varied.<sup>6, 46</sup>

None of the major categories of anaerobic pathogens currently demonstrates any significant resistance to chloramphenicol. In a study en-

compassing 601 clinical isolates and representing the entire spectrum of clinically important anaerobes, 6.2 micrograms per ml. of chloramphenicol inhibited all save 5 strains (1 of *B. terebrans*, 2 of *Peptococcus* sp., and 2 of *B. fragilis*, and the latter 2 were inhibited by 12.5 micrograms per ml.).<sup>30</sup> In this same survey, only 1 strain each of *B. incom-  
munis*, *Clostridia* sp., and *Fusobacterium* sp. as well as 6 of 145 strains of peptococci were not inhibited by 3.1 micrograms per ml. of clindamycin. *F. varium* species are somewhat more resistant to clindamycin.<sup>3, 11</sup> However, *Clostridium* species other than *C. perfringens*, particularly *C. sporogenes* and *C. tertium*, commonly recovered from gas gangrene and anaerobic cellulitis secondary to war wounds, are somewhat more resistant to clindamycin, requiring from 6.2 to more than 12.5 micrograms per ml. for inhibition.<sup>53</sup>

Clostridial infection not responding to clindamycin therapy has been reported.<sup>49</sup> In one study of 43 strains of *C. perfringens*, there was good correlation between the agar dilution and the paper disc diffusion results, although zones of inhibition around the standard 2 microgram clindamycin discs were small, and results more easily interpreted with a 10 microgram disc.<sup>10</sup> Carbon dioxide does not affect the minimum inhibitory concentrations of clindamycin.<sup>25</sup>

Proof of the efficacy of chloramphenicol in anaerobic infections, including those caused by bacteroides, is largely testimonial, and sometimes disputed<sup>23</sup> because of the problem in evaluating the role of a single antibiotic in these complicated, polymicrobial infections in which surgery often plays a prominent role.<sup>5</sup> The efficacy of clindamycin is suggested in a number of recent reports; poor cerebrospinal fluid penetration may limit its usefulness in infections of the nervous system, however.<sup>3, 8, 17</sup>

## ANTIBIOTICS OF SELECTIVE USEFULNESS

In the absence of proven or suspected *B. fragilis* infection, certain other antibiotics may be valuable in the management of patients with anaerobic infections. Not all these drugs have been studied as thoroughly in vitro as others, and as noted in some instances laboratory techniques have differed. For many organisms, the exact distinction between susceptible and resistant is far from settled, although in general the figures cited most commonly derive from those serum concentrations usually achieved with standard doses of drug.

### Tetracyclines

Although tetracycline was once considered the drug of choice for bacteroides infections, a number of studies have now firmly established the emerging resistance of *B. fragilis* to this drug and its analogues.<sup>32</sup> In a representative study, more than half of Kislak's 40 *B. fragilis* strains had minimum inhibitory concentrations of 12.5 micrograms per ml. or greater for tetracycline and, although doxycycline and methacycline were somewhat more active, at least 25 per cent of these strains had minimum inhibitory concentrations of 12.5 micrograms per ml. or greater for these newer analogues.<sup>25</sup> *B. fragilis* strains demonstrate a bimodal

distribution of sensitivities to the tetracyclines, readily identified even by paper disc diffusion studies in which results agree closely with agar dilution studies.<sup>6, 25, 30, 45</sup>

A significant percentage of peptococci (38 per cent) and peptostreptococci (23 per cent) were not suppressed by 6.2 micrograms per ml. of tetracycline in one large survey,<sup>30</sup> and some<sup>22, 30</sup> but not all<sup>10</sup> reports suggest resistance of 10 to 15 per cent of *C. perfringens (welchii)* to this concentration of tetracycline, with doxycycline and minocycline somewhat more active in vitro and again good correlation between agar dilution and paper disc susceptibility test results.<sup>10</sup> Selected strains of microaerophilic cocci, *F. varium*, and *Eubacterium* are also resistant.<sup>13</sup> Although 83 per cent of *B. melaninogenicus* strains, representing primarily oral rather than intestinal bacteroides species, had minimum inhibitory concentrations of 6.2 micrograms per ml. for tetracycline, this drug lacks sufficient breadth of in vitro activity to place it in a first choice category for anaerobes;<sup>30</sup> doxycycline and minocycline are somewhat more active in vitro, but have not been studied as yet in vivo.

### Erythromycin

In two studies, 95 to 100 per cent of *B. fragilis* strains were inhibited by 0.1 to 6.2 micrograms per ml. (mean of 1.6 micrograms per ml.) of erythromycin.<sup>25, 30</sup> Differences in methodology (media, age of cultures, and length of incubation) may account for findings in a third survey where only 39 per cent of 122 *B. fragilis* strains had minimum inhibitory concentrations of 6.2 micrograms per ml. of erythromycin.<sup>46</sup> The presence of 10 per cent carbon dioxide increases the minimum inhibitory concentrations for erythromycin 4 to 32-fold, presumably by influencing the inoculum or lowering the pH of the agar.<sup>20, 21</sup> Some *B. fragilis* subspecies (*B. variabilis*, *B. incommunis*) and *B. oralis* are somewhat more resistant in vitro to erythromycin and minimum bactericidal concentrations for *B. fragilis* are 16 times greater than minimum inhibitory concentrations.<sup>30</sup>

*B. melaninogenicus* is uniformly susceptible to 1.6 micrograms per ml. of erythromycin,<sup>30</sup> but only 72 per cent of 43 *C. perfringens* strains were inhibited by a concentration of 3.12 micrograms per ml., with poor correlation between agar dilution and paper disc susceptibility results in one study,<sup>10</sup> whereas 100 per cent of 34 strains (and all 17 *Clostridium* sp.) were inhibited by this concentration in another study.<sup>30</sup> Most gram-positive anaerobic cocci and non-sporeforming rods and some fusobacteria are inhibited by 6.2 micrograms per ml. of erythromycin; most fusobacteria and *Veillonella* species are more resistant, however.<sup>11, 28, 30</sup>

### Lincomycin

The parent compound for clindamycin is considerably less active in vitro, resembling erythromycin with only minor differences. All but a few *B. fragilis* strains were considered quite sensitive to lincomycin in concentrations of 3.1 to 6.2 micrograms per ml. in two studies,<sup>25, 30</sup> but in a third laboratory, only 57 per cent of 122 strains were inhibited by 6.2 micrograms per ml. and only 13 per cent were considered sensitive (defined as 3.1 micrograms per ml.).<sup>46</sup> In this latter study, the zone of

inhibition surrounding 2 or 10 micrograms lincomycin discs correlated poorly with agar dilution results because of considerable overlapping among sensitive, intermediate, and resistant organisms. The minimum inhibitory concentrations for lincomycin are also increased by a factor of 4 to 32 in the presence of added carbon dioxide.<sup>20, 21</sup>

*Clostridium* species (other than *C. perfringens*) are somewhat less, and peptococci and *Veillonella* sp. somewhat more, susceptible to lincomycin than to erythromycin; otherwise their in vitro susceptibility patterns are quite similar.<sup>30, 40</sup> Although lincomycin has demonstrated usefulness in a limited number of reports, clindamycin has probably supplanted it for most purposes.<sup>3</sup>

### Penicillins and Cephalosporins

Only a small percentage of *B. fragilis* strains are susceptible to conventional concentrations of penicillin G, but 83 per cent of *B. melaninogenicus* strains are inhibited by 1.6 micrograms per ml.<sup>6, 24, 25, 30, 46</sup> Rare strains of *Fusobacterium* are resistant.<sup>11, 13</sup> Ampicillin behaves in similar fashion, while carbenicillin exerts somewhat greater activity against *B. fragilis* at those concentrations readily attained by the large doses customarily employed—35 per cent suppressed by 25 micrograms and 75 to 85 per cent by 50 micrograms per ml.<sup>6, 25</sup> There has been no reported clinical application of the latter finding, as yet. Activity of the semisynthetic penicillinase-resistant penicillins (methicillin, oxacillin, nafcillin, cloxacillin, and dicloxacillin) against *B. fragilis* strains is negligible.<sup>25</sup>

The cephalosporins, save cephaloridine,<sup>13</sup> are less active than penicillin G and ampicillin against *B. fragilis*.<sup>6, 25, 30</sup> Only occasional strains of other anaerobes, excluding *B. fragilis*, are not inhibited by 1.6 to 3.1 micrograms per ml. of penicillin; this includes all clostridia, anaerobic cocci, *Veillonella* and various non-sporeforming gram-positive rods, including actinomyces.<sup>28, 30, 42</sup> Ampicillin and carbenicillin have not been tested against all these other pathogens, but cephalothin is less active than penicillin G against *F. fusiforme*, *Eubacterium lentum* and *Bifidobacterium* sp.<sup>30</sup>

Other cephalosporin compounds have not been broadly studied, although cephaloridine was demonstrated to be the most, and cephalixin the least, active against *C. perfringens*<sup>50</sup> and actinomyces.<sup>28</sup> Thus, among the penicillins and cephalosporins, when confronting anaerobes other than *B. fragilis*, penicillin G would appear to be a drug of choice, with no known advantage to selecting any related drug except possibly cephaloridine in the presence of penicillin hypersensitivity. Carbenicillin may prove of value in *B. fragilis* infections, pending further studies. Whether certain *B. fragilis* infections might respond to larger than conventional doses of penicillin or penicillin-like drugs remains unanswered.<sup>24</sup>

### LEAST ACTIVE DRUGS

Polymyxins, previously, and aminoglycosides, both previously and currently, represent drugs of choice for many gram-negative infections where anaerobes may be present but go undetected. Therefore, it is most

important to bear in mind that for practical purposes, they are inactive against all of the major anaerobic pathogen categories.

Both kanamycin and gentamicin suppress only occasional strains of *B. fragilis* at a concentration of 25 micrograms per ml. and only a third of *B. melaninogenicus* strains at reasonable concentrations—0.4 to 1.6 micrograms per ml.<sup>30</sup> Neither is significantly active against clostridia<sup>30, 51</sup> or anaerobic cocci, although gentamicin suppressed 20 to 30 per cent of peptococci or peptostreptococci in concentrations of 3.1 to 6.2 micrograms per ml. in one study.<sup>30</sup> Except for some limited activity against *Eubacterium lentum*, both aminoglycosides are relatively inactive against gram-positive non-sporeforming rods, including actinomyces.<sup>28, 30</sup>

Streptomycin and polymyxins are also inactive against *B. fragilis* strains, even in concentrations in excess of 100 micrograms per ml.<sup>25</sup> The polymyxins (polymyxin B and polymyxin E or colistin) are quite active against certain gram-negative anaerobic bacilli, such as *B. oralis*, *B. melaninogenicus*, and *F. nucleatum*, but there has been no clinical experience in managing anaerobic infections with these drugs and they diffuse poorly into tissues and body spaces.<sup>11</sup>

## INVESTIGATIONAL ANTIMICROBIALS

### Rifampin

Clinical studies are pending, but this drug holds considerable promise on the basis of its in vitro activity. All *B. fragilis* strains are suppressed at a concentration of 1.6 to 3.1 micrograms per ml. or less,<sup>25, 30, 32, 56</sup> but there is a tendency for rapid one-step resistance, as manifested by the skip-tube phenomenon when minimum inhibitory concentrations are determined in broth dilution studies; rifampin is irregularly bactericidal.<sup>21, 32, 56</sup> Some strains of *Fusobacterium*, *Eubacterium*, and clostridia are resistant to rifampin,<sup>11, 30, 47</sup> but 89 to 100 per cent of 601 representative anaerobic pathogens were inhibited by 1.6 micrograms per ml. or less.<sup>30</sup> Actinomyces are highly susceptible to rifampin.<sup>28</sup> Minimum inhibitory concentrations for rifampin are not altered in the presence of carbon dioxide.<sup>21</sup>

### Metronidazole

Recent reports suggest that this heterocyclic nitro compound, useful in *Trichomonas* infections and amebiasis, possesses considerable in vitro activity against anaerobic pathogens.<sup>11, 32, 48</sup> Most anaerobic strains are inhibited by 6.2 micrograms per ml. or less of metronidazole.<sup>48</sup> In one study, 54 strains of *B. fragilis* were inhibited by 0.2 to 6.25 micrograms per ml. of metronidazole, with minimum bactericidal concentrations of 0.78 to 6.25 micrograms per ml., making it the most consistently bactericidal drug for *B. fragilis* thus far studied.<sup>32</sup> It is consistently active against *F. varium*, the most resistant of all gram-negative anaerobic bacilli other than *B. fragilis*.<sup>11</sup> These investigators cited some previous limited in vitro and in vivo references, but to date no other significantly broad in vitro studies of metronidazole have been reported. Early clinical experiences are encouraging.<sup>48</sup> Metronidazole has limited activity against a variety of

pathogenic actinomyces species, including *A. israelii*, in concentrations ranging from 50 to 100 micrograms per ml.<sup>28</sup> and against certain strains of microaerophilic cocci.<sup>13</sup>

### Vancomycin

*B. fragilis* strains are resistant to this seldom used antibiotic,<sup>32, 46</sup> but it is active against a number of gram-positive anaerobic organisms, such as *C. perfringens*,<sup>40</sup> microaerophilic and anaerobic cocci,<sup>13</sup> and almost 100 per cent of pathogenic actinomyces in concentrations of 2 to 20 micrograms per ml.<sup>28</sup>

### SUMMARY

Although evaluating the role of antibiotics alone in the management of anaerobic infections is difficult, because of polymicrobial involvement and the frequent necessity to resort to surgical intervention, it is possible to identify the most and the least useful drugs on the basis of current in vitro data and collected clinical experience. Chloramphenicol and clindamycin are clearly the drugs of choice for the moment, although rifampin and metronidazole deserve further study and clinical trials. Penicillin G, ampicillin, and cephaloridine are comparable in vitro, and can be used for all anaerobic infections except those involving *B. fragilis* and rare strains of *Fusobacterium*.

Lincomycin, erythromycin, and tetracyclines offer no great advantage over penicillin G, in situations in which *B. fragilis* is not involved, unless penicillin or cephalosporin hypersensitivity is a consideration. The aminoglycosides and polymyxins are essentially inactive against this large and diverse group of pathogens.

### ACKNOWLEDGMENT

The author would like to thank Dr. Sydney M. Finegold for his thoughtful review of this manuscript.

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## Urinary Tract Infection

### Problems in Diagnosis and Management — 1973

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Recurrent urinary tract infections present a challenging diagnostic and therapeutic problem. They rank second in frequency of occurrence only to upper respiratory infections. The incidence of chronic pyelonephritis reported in autopsy series varies from 2.8 to 15 per cent, yet the diagnosis, prior to death, was much less frequent than would be indicated by these autopsy findings.<sup>12, 14</sup> This could be due to the occurrence of many asymptomatic cases of chronic pyelonephritis or due to the fact that pathologic findings similar to those seen in chronic pyelonephritis can be produced by a number of factors.

Pyelonephritis is a disease continuum. The initial event may well occur in childhood; however, the majority of children who develop severe renal damage as a consequence of urinary tract infection usually have some associated obstructive lesion.

#### DEFINITION OF TERMS

*Chronic interstitial nephritis* is a term used to designate renal disease with histologic findings of chronic pyelonephritis but no evidence for bacterial infection.<sup>3</sup> The pathologic hallmark is cellular infiltration of the interstitium with lymphocytes and plasma cells. There is usually tubular atrophy, foci of dilated tubules filled with colloid casts, glomeruli which in scarred areas may be sclerotic but in other areas may look normal and arteries and arterioles that show medial hyaline changes and intimal proliferation. These histologic findings may be produced by a number of conditions, including analgesic abuse,<sup>28</sup> potassium depletion,<sup>24</sup> vascular lesions,<sup>15</sup> and uric acid deposits.<sup>7</sup>

*Chronic pyelonephritis* is chronic interstitial nephritis produced by bacterial infection. The change in the kidney which seems to be most specific for damage caused by bacteria consists of a broad scar in the renal cortex associated with retraction of the corresponding renal papillae.<sup>9</sup>

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*Acute pyelonephritis* is usually a clinical symptom complex associated with bacteria in the urine. Histologic examination of the kidneys would simply show the accumulation of polymorphonucleated white blood cells around and within the renal tubules. The symptoms are usually irritative bladder symptoms associated with chills, fever, and flank pain.

*Urinary tract infection* refers simply to the finding of microorganisms in the urine with or without clinical symptoms and with or without evidence of renal disease. This is a generic term which includes asymptomatic bacilluria, cystitis, and pyelonephritis.

## PATHOGENESIS

The normal urinary tract is sterile except for the distal urethra in both the male and female. There is now considerable evidence that supports the ascending route as the most important pathway of entry for bacteria into the urinary tract.<sup>25</sup> Studies of urethral and vaginal vestibule cultures of normal females may occasionally yield gram-negative bacilli, but when present they are there in very small numbers. However, in females with recurrent urinary tract infections, Stamey's studies have clearly demonstrated the establishment of enterobacteria in the vaginal vestibule in significant numbers just prior to an episode of a urinary tract infection. It would thus appear that the microflora of the vaginal vestibule is an important predecessor in the development of the urinary tract infection.

Once infection develops in the bladder, bacteria can easily reach the upper urinary tract. There is a fluid connection between the kidney and the bladder through the ureters and it is very easy for bacteria to involve the upper urinary tract, with or without gross reflux of urine.

In the male patients, spontaneous infection can and does occur without previous instrumentation. The prostate, however, is the most important factor in recurrent or persistent urinary tract infection. Chronic bacterial prostatitis may persist in the presence of a sterile urine and be the source of reinfection. There are currently no antibiotics, effective against gram negative bacilli, which are concentrated in prostatic fluid, so it is exceedingly difficult to eradicate bacterial prostatitis. Trimethoprim, an antibacterial substance, is a lipid-soluble base which has been shown to be concentrated in prostatic fluid.<sup>26</sup> It has been combined with sulfamethoxazole (Bactrim<sup>®</sup> and Spectra<sup>®</sup>) and may prove useful in treating bacterial prostatitis.<sup>29</sup>

## DIAGNOSIS OF URINARY TRACT INFECTION

History may be helpful in making the diagnosis when one can elicit the typical story of irritative bladder symptoms consisting of frequency, dysuria, and urgency. In children the presenting symptoms may be

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atypical, such as fever of unexplained origin or failure to thrive. It is always important to obtain a history of the voiding pattern of the patient to be sure that he is not an infrequent voider and that he voids without any obstructive symptoms. The history, of course, will not be of help in the patient with asymptomatic bacilluria.

### LABORATORY AIDS

#### Urinalysis

On routine examination of the urine in patients with urinary tract infections proteinuria is usually absent. Even in advanced chronic pyelonephritis the amount of protein excreted in the urine rarely exceeds 2 to 3 gm. per 24 hours. In acute infections, white blood cells are usually present and will be a helpful clue, but in chronic urinary tract infections, "significant" pyuria is often absent. Thus the diagnosis of a urinary tract infection cannot be based solely on the presence or absence of white blood cells in the urinary sediment. Red blood cells are usually absent in urinary tract infections unless there is a hemorrhagic cystitis and then the urine may be grossly bloody. Casts are rarely seen but if white blood cell casts are present this usually means that the renal parenchyma is involved in the infectious process.

A methylene blue or gram stain of the urinary sediment is a useful way to look for bacteria. If bacteria are present in the first morning voided, unspun urinary specimen, this represents a significant bacilluria (greater than 10,000 colonies per ml.). In centrifuged specimens this statement may not always be accurate. In our experience, the stained sediment is accurate about 80 per cent of the time with errors being made in not identifying bacteria when significant bacilluria is present and in sometimes identifying bacteria which are not true pathogens.

Screening tests for bacteria such as the Greiss nitrate test<sup>11</sup> or the triphenyl-tetrazoleum chloride (T.T.C.) test<sup>12</sup> are not sensitive enough to be depended upon for identifying all patients with significant bacilluria. They show a positive test when more than  $10^5$  bacteria per ml. are present but may give a negative test when smaller but significant numbers of bacteria are present.

#### Quantitative Urine Cultures

These are the most valuable laboratory aids in the diagnosis of patients with significant bacilluria. The technique of collecting the specimen is the key to success in quantitative urine cultures. Direct suprapubic aspiration of bladder urine under sterile conditions is the most reliable technique of obtaining urine for culture but simply is not practical to use in a busy clinical practice. Urethral catheterization will probably be 95 per cent accurate and the risk of introducing infection with a single catheterization is less than 1 to 2 per cent in the female.<sup>27</sup>

Voided urine specimens, when properly collected, can also be quite accurate and this is our method of choice for children and all males. Kass and his co-workers have established that a single culture of a voided urine specimen containing greater than  $10^5$  bacteria per ml. has an 80 per

cent chance of representing a significant urinary tract infection. Two consecutive specimens with the same colony count raise the accuracy to 95 per cent and the confidence level can be increased still further by obtaining additional voided specimens.<sup>11</sup> It is our belief that a single properly collected mid-stream voided specimen collected by specially trained nurses will approach the 95 per cent level of confidence.

The number of bacteria in a quantitative urine culture which indicates a significant urinary tract infection varies with the method of collection. Using a specimen collected by suprapubic aspiration the urine should be sterile and any growth of bacteria is significant. In well collected midstream clean-voided specimens or catheterized specimens,  $10^5$  bacteria per ml. of urine are definitely significant as shown by Kass<sup>10</sup> but counts of 10,000 colonies may also be significant. Colony counts of 1,000 colonies per ml. must be carefully evaluated in relation to the method of collection and to the type of organism cultured. Repeating the quantitative urine culture is usually advisable on patients when the diagnosis is in question before initiating therapy.

#### LOCALIZATION STUDIES

History and physical examination are sometimes helpful in predicting bacteriologic involvement of the kidneys. There are methods, however, which will help the clinician more accurately determine if the renal parenchyma is involved. These include urographic abnormalities suggesting inflammatory disease, loss of renal function, particularly the ability to concentrate the urine, and histologic examination of the tissue obtained by renal biopsy. Stamey's technique with ureteral catheters is probably the most accurate method for identifying bacterial involvement of the upper urinary tract.<sup>29</sup> The technique is seldom used in clinical practice since it is tedious and the information obtained is usually not required in determining the best treatment for the patient. In general, when a patient has significant bacilluria and inflammatory changes on the intravenous pyelogram, it is safe to imply that the renal parenchyma is involved in the inflammatory process.

#### EVALUATION OF THE PATIENT

The first episode of a urinary tract infection in the male should be an indication for a thorough urologic evaluation. In the female with the first urinary tract infection some basic screening studies should be done in addition to history and physical examination. These include a urinalysis, quantitative urine culture, and evaluation of renal function. The female is then treated and followed carefully. If the infection persists or recurs, complete urologic investigation is indicated.

Urologic evaluation of the patient with recurrent or persistent urinary tract infection must begin with an intravenous pyelogram. In the male at the time of the intravenous pyelogram, a voiding cystourethrogram should also be obtained with a post-voiding film. The residual urine

is usually checked, and if voiding symptoms suggest a neurogenic bladder, a cystometric examination is performed while the catheter is in place. This is followed immediately by a voiding cystourethrogram to determine whether there is reflux of urine into the upper urinary tract, to evaluate the vesical neck and urethra, and to determine the ability of the bladder to empty effectively. Urine specimens may be sent for culture for tuberculosis and for cytology in selected patients. Cystoscopy with urethral calibrations and retrograde pyelograms, if needed, are then carried out. The quality of the intravenous pyelography that can now be obtained has minimized the need for retrograde pyelograms. In selected patients, renal biopsy with culture of the tissue removed as well as renal angiography may occasionally be indicated.

If all urologic studies are normal, treatment of the urinary tract infection is started. If an abnormality of urinary tract is detected, this should be corrected, if possible, before initiating chemotherapy.

### RATIONALE FOR TREATMENT

Acute uncomplicated urinary tract infections can be treated effectively with nearly any drug and cured in about 80 per cent of patients. The drug of choice is usually a sulfonamide or nitrofurantoin, unless sensitivity studies suggest that other antibiotics should be used. The patient should return in 3 to 4 weeks for a urinalysis and quantitative urine culture. If these are negative, future periodic checks utilizing urinalysis and quantitative urine cultures are advised. If the urinary tract infection fails to clear, further urologic investigation should be carried out before placing the patient on long-term chemotherapy.

The results obtained in chronic or recurrent urinary tract infection have not been as good as those obtained in the simple uncomplicated infection.

**SHORT-TERM THERAPY.** In a series reported by McCabe and Jackson<sup>22</sup> of 252 patients who were treated with the drug of choice for 10 to 14 days, the urine culture became sterile in 80 per cent during therapy. However, in the follow-up period, after stopping chemotherapy only 32 per cent continued to have sterile urines. Twenty-six per cent of these patients suffered relapse with the same strain shortly after stopping therapy. Reinfection with a new strain of bacteria tended to occur at a later date.

**INTERMEDIATE THERAPY.** Turck and co-workers<sup>22, 33</sup> treated a group of patients for 6 weeks with the most effective antibiotic as determined by culture and sensitivity studies. Sixty-two per cent of their patients had sterile urine cultures during the first 10 to 14 days of treatment. At the follow-up check 6 weeks after stopping chemotherapy, only 20 per cent of their patients continued to have a sterile urine.

**LONG-TERM THERAPY.** It would appear from the preceding studies that it is possible to sterilize the urine in a large majority of patients with chronic urinary tract infection but the problem remaining is to then keep the urine sterile over a long period of time. The source of reinfection or relapse is probably from the perineal area in the female patient and from

the prostate gland in the male patient.<sup>29</sup> In addition, there may be areas in the renal medulla which retain bacteria that may later produce reinfection.

Data supporting the concept of long-term therapy of recurrent or persistent urinary tract infection has been rather scarce. In 1968 Freeman and co-workers reported a study of continuous long-term chemotherapy used in treating 122 males.<sup>2</sup> Initial treatment was with the drug of choice for a period of 10 days. Urine cultures were obtained 4 days after each patient was started on the therapy, and if the urine was not sterile or showed more than 1000 colonies per ml. of urine, another course of a specific drug, selected from data obtained with culture and sensitivity studies, was given. The investigators were required to give at least three courses of specific chemotherapy before the patient was termed a preliminary antibiotic treatment failure.

On the last day of the specific antibiotic therapy the patient was then placed on one of four treatment regimens for long-term management: (1) sulfamethizole, 0.5 gm. four times daily; (2) nitrofurantoin, 50 mg. four times daily; (3) methenamine mandelate, 1.0 gm. four times daily, and (4) placebo tablets, four times daily. It was arbitrarily planned to treat these patients for 25 months or until signs of toxicity occurred. All patients were seen at periodic intervals for urinalysis, urine cultures, and creatinine clearance. At 13 and 25 months the patients were to undergo complete re-evaluation.

Results obtained with the preliminary therapy showed that 67 per cent of patients with *Pseudomonas* infections and 78 per cent of patients with mixed infections had sterile urines during the initial treatment program. The response of organisms of the *E. coli*, *Klebsiella* and *Aerobacter* group ranged between 89 and 100 per cent. This again supported the earlier demonstrated concept that with good initial chemotherapy it is possible to sterilize the urine in a high percentage of patients with chronic urinary tract infections. During the follow-up period, interim specific antibiotic therapy was instituted if the urine culture became infected while on the long-term chemotherapy and 37 of the 122 patients required this type of chemotherapy. After 13 months of treatment the percentage of patients with sterile urines in the four groups were as follows: (1) sulfonamide, 67 per cent, (2) nitrofurantoin, 64 per cent, (3) methenamine mandelate, 78 per cent, and (4) placebo, 14 per cent. Toxic reactions to the various drugs were minimal.

In an ongoing study with children, Straffon and co-workers report a similar result with long-term chemotherapy in a group of 92 children.<sup>31</sup>

## PLAN OF TREATMENT

An acute uncomplicated urinary tract infection should be treated with either a sulfonamide or nitrofurantoin for 14 days. The patient should then be seen in 3 to 4 weeks to be sure the urine is sterile, after which he is followed at periodic intervals with urinalysis and urine cultures. If the infection fails to clear, complete urologic investigation is carried out before any additional therapy is started. All male patients

deserve a thorough investigation at the time of their first urinary tract infection.

Patients with recurrent or chronic urinary tract infections must have a thorough urologic evaluation as has been outlined previously before starting long-term chemotherapy. If surgical intervention is required to improve the response of the chemotherapy, this should be done. If the study indicates that there is nothing to be gained by an operative procedure the patient should be placed on the following chemotherapy program. The drug of choice is selected from the culture and sensitivity studies and the patient is treated for 14 days with this specific drug. This is immediately followed by using either a sulfonamide, nitrofurantoin, or methenamine mandelate. When methenamine mandelate is used, the urinary pH should be monitored with nitrazine paper and ascorbic acid added to the regimen in whatever dose is required to keep the urinary pH below 6.0.

The patient is seen and evaluated at 6 weeks and if still infected a second course of specific chemotherapy is given for 14 days. Future periodic checks are then made, usually at 2 to 3 month intervals. If three consecutive urine cultures are sterile, the dosage of the drug used in the long-term chemotherapy is reduced, and if the urine remains sterile, the medication is discontinued and the patient is followed with periodic urine cultures at progressively longer intervals. In some females intermittent chemotherapy may be used, giving the medication only at high risk periods such as after intercourse or during their menses. If the patient's urine remains infected, re-evaluation is done at 1 year to reassess the entire urinary tract. Careful and prolonged follow-up of patients is the cornerstone of long-term chemotherapy.

## THE ROLE OF SURGERY

Any surgical procedure performed on a patient with recurrent chronic urinary tract infection should be considered an adjunct to chemotherapy. There are several groups of patients in which surgery may be required.

### Congenital Anomalies

There are certain congenital anomalies which produce obstructive lesions which must be corrected before a urinary tract infection can be eradicated. An example of this is a duplication anomaly of the kidney in which the ectopic ureter is obstructed and must be treated by either ureteroneocystostomy or heminephroureterectomy. Another example would be a urethral valve in a young child, which can produce severe obstructive changes.

### Reflux

Reflux is certainly not a normal finding in adults. In children under 3 years of age, the incidence of reflux has been reported by Kollerman and Ludwig to be 30 per cent.<sup>16</sup> Lich and co-workers<sup>18</sup> reported a very low incidence of reflux in the newborn, and others<sup>23</sup> have shown that in older

children with normal urinary tract there is again a low incidence of ureteral reflux.

In children with urinary tract infection, reflux is quite common, ranging from 19 per cent in Kunin's<sup>17</sup> series to 55 per cent in Govan and Palmer's paper.<sup>2</sup> On the other hand, reflux is not common in adult females with urinary tract infection. Baker's data<sup>1</sup> on 210 consecutive adults with urinary tract infections who were studied for reflux at the time of their initial examinations reveals that a history of urinary tract infection was obtained in 74 per cent of these patients and that 5.7 per cent of this group showed reflux.

When the percentage of children in each age group showing reflux are plotted against the age of the group under study, reflux was found in 70 per cent of all children under 1 year of age, 50 per cent at 1 year of age, and thereafter the incidence of reflux gradually decreased to 5 per cent for adults.<sup>1</sup> This data suggests that 80 per cent of children with reflux will not have this when they become adults. Neither death nor surgical correction can account for this reversal in the groups studied.

Finally, reflux does not seem to be related to obstruction. Stephens and Lanaghan could find no correlation between the incidence of reflux and obstruction.<sup>30</sup> The question remains, does reflux in the presence of a sterile urine produce renal damage? Evidence supports the concept that reflux of sterile urine without associated obstruction does not cause progressive renal damage. Stephens and Lanaghan studied 34 patients with reflux for 5 to 10 years and found no evidence of deterioration in renal function.<sup>30</sup> Fritjofsson and Sundin studied renal function in 9 patients with unilateral reflux for a period of 1 to 11 years.<sup>4</sup> Six patients without infection showed no change on the refluxing side as compared with the contralateral side, while 3 patients with repeated urinary tract infections showed deterioration of the refluxing side. Data obtained in our study of children would support this finding.<sup>31</sup>

With these data in mind, our current plan of therapy is to treat patients with normal upper urinary tracts as determined by intravenous pyelogram, with or without reflux, with specific chemotherapy followed by long-term chemotherapy as previously described. If the infection clears and the urine culture remains sterile, the patient is followed carefully with periodic renal function studies, urine culture, and intravenous pyelogram. If the infection fails to clear, continues recurring, or if the intravenous pyelogram shows evidence of obstructive changes with or without reflux, ureteroneocystotomy should be performed to aid in the therapy of the infection.

### **Vesical Neck Obstruction**

Some years ago this was felt to be a common etiologic factor in recurrent or persistent urinary tract infections in females.<sup>21</sup> It is our current belief that this is rarely seen in female patients and vesical neck plasty is seldom performed to aid in the treatment of recurrent or persistent urinary tract infections.

### **Distal Urethral Stenosis**

This is a term introduced by Lyons and Smith in 1963, and refers to a ring of resistance noted in the distal third of the female urethra when a

bougie à boule is passed through the area.<sup>19</sup> Great success in clearing urinary tract infections has been reported following dilation of this area of resistance.<sup>20</sup> Graham and co-workers compared the calibration of the urethra in a series of infected and uninfected females and found little difference in urethral size between the two groups.<sup>5</sup> It is our belief that this area of narrowing is usually seen in youngsters with long-standing or recurrent urinary tract infection and represents inflammatory change. The urethra is routinely calibrated and dilated at the time of the initial cystoscopic examination. Subsequent urethral dilations are seldom required.

### Supravesical Diversion

Supravesical diversion with cutaneous ureterostomy or an ileal conduit is sometimes indicated when urinary tract infections are associated with severe bilateral hydronephrosis and renal insufficiency. These procedures, by providing better drainage, may stabilize renal function for patients in whom their renal function has been gradually deteriorating because of obstruction and infection.

## CONCLUSION

The successful management of urinary tract infection requires the skillful blending of chemotherapy and surgical intervention. When these modalities are properly applied, a successful result will be achieved in the majority of patients with recurrent or chronic urinary tract infections.

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# Pneumonias Acquired Outside the Hospital

## Recognition and Treatment

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Pneumonia continues to have a major impact on the medical resources of this country. According to Metropolitan Life Insurance Company statistics, pneumonia is the fifth leading cause of death in the United States, and remains the most common infectious cause of death.<sup>16</sup> Since the introduction of the antibiotics, the number of hospital admissions for pneumonia had shown an annual decline until the early 1950's, but this trend has stopped and the number of both admissions and deaths resulting from pneumonia appears to have stabilized.<sup>17</sup>

Pneumonia acquired outside the hospital often presents diagnostic and therapeutic problems which differ considerably from the pneumonias which develop in predisposed hospitalized patients. Pneumonias acquired outside the hospital frequently occur in otherwise healthy persons and usually are caused by viruses, pneumococci, or *Mycoplasma pneumoniae*. Occasionally, these pneumonias are caused by other organisms and unusual pathogens. Depending upon the pathogen and other circumstances, the clinical course may range from mild, self-limited illness to rapidly lethal disease. For some of these pneumonias, antimicrobial therapy is required for cure and for others it is not. Thus it is important to try to establish an etiologic diagnosis in order to make appropriate decisions concerning therapy.

The purpose of this paper is to discuss the infectious pneumonias acquired outside the hospital, to review criteria for the diagnosis of specific infections, and to outline an approach to management.

### GENERAL CONSIDERATIONS

Classically, pneumonia has been categorized in descriptive anatomic terms such as lobar, bronchopneumonia, and interstitial pneumonia. Cur-

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rently, it seems more appropriate for clinicians to classify pneumonia according to the agent which is responsible for provoking the inflammatory process occurring in the alveoli and adjacent pulmonary structures. Parenchymal lesions in the lung can be incited by inanimate agents such as radiation, oils, acids, noxious gases, other chemicals, and pollutants, as well as by living agents such as bacteria, viruses, mycoplasma, rickettsiae, chlamydiae, fungi, and protozoa. Other disorders such as pulmonary infarction, pulmonary embolus, allergic pneumonitis, congestive heart failure, tumors, uremia, and sarcoidosis must also be considered in a patient with evidence of pneumonia. Therefore, it is important to think in terms of broad etiologic categories and to attempt to separate the noninfectious from infectious causes.

Incorrect etiologic diagnosis of infectious pneumonia may lead to administration of inappropriate antimicrobial drugs with disastrous consequences—fatal infection caused by inadequate treatment or serious toxic or allergic reactions in patients with self-limited viral diseases. Accordingly, steps must be taken to establish an etiologic diagnosis of the pneumonia in order to avoid such complications. It is very important to attempt to establish whether or not infectious pneumonia is of bacterial or nonbacterial etiology. Some of the distinguishing clinical features are listed in Table 1.

To establish an accurate etiologic diagnosis, data from several sources need to be evaluated. The investigation is initiated by taking a careful history. It is important to characterize the prodrome and mode of onset of the disease, the number, frequency, and duration of chills, the character of chest pain, and other medical problems, and to document recent antimicrobial therapy. It is imperative to gather epidemiologic data concerning illnesses in the family, family members recently home from the hospital, type and place of employment, and recent travel. It is also important to inquire about social habits such as alcohol, tobacco, and drug abuse.

A careful physical examination demonstrating rales, signs of consolidation or pleural effusion, and extrapulmonary signs of infection is essential. Both lateral and posteroanterior x-ray films of the chest are necessary

**Table 1. Characteristics of Pneumonias  
Acquired Outside the Hospital**

	BACTERIAL	VIRAL OR MYCOPLASMA
Onset	Sudden	Gradual
Chills	Common	Uncommon
Fever	High	Low-grade
Tachycardia (>120/min.)	Common	Rare
Tachypnea (>30/min.)	Common	Rare
Chest pain	Common	Uncommon
Sputum	Purulent, abundant	Mucoid, initially scant
Lobar or segmental consolidation	Common	Rare
Significant pleural effusion	Relatively common	Rare
Polymorphonuclear leukocytosis	Common	Uncommon

Table 2. *Gram Stain—Rapid Method*

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1. Air-dry sputum on slide	6. Wash
2. Heat-fix slide to a temperature just tolerable to skin on back of hand	7. 95% ETOH—decolorize
3. Crystal violet—10 seconds	8. Wash
4. Wash	9. Safranin—10 seconds
5. Lugol's iodine—10 seconds	10. Wash and blot dry

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to localize the process and to confirm the presence or absence of fluid. Although the chest x-ray rarely suggests a specific etiologic agent, it can provide important clues and may reveal the presence of unsuspected pleural fluid which, on examination by Gram stain and culture, may yield the specific etiologic agent.

A Gram stain of the sputum is imperative. If indicated, an acid-fast stain for *Mycobacterium tuberculosis* and a wet mount for fungi should be done as well. These preparations should be examined by the physician and not just by laboratory personnel, because appropriate areas of the smear must be examined. The organisms which are etiologically significant are associated with and ingested by polymorphonuclear leukocytes. The organisms associated with and attached to squamous epithelial cells derived from the buccal mucosa are mouth flora and are not significant.

Occasionally, for a variety of reasons such as dehydration, lack of cooperation, and/or depressed level of consciousness, it may be difficult to obtain an expectorated sputum. In this instance, nasotracheal suction or transtracheal aspiration should be employed to obtain a specimen. The Gram stain can be done utilizing the one-minute rapid technique, and need not be a burden with respect to time (Table 2).

Unfortunately, the sputum smear may show a mixed flora without a predominant organism. Similar results may also be found by sputum culture.<sup>21</sup> It is important, therefore, to obtain blood cultures in every patient with pneumonia and to perform thoracentesis whenever there is pleural effusion. Since it is extremely rare to find more than one type of organism in the blood or pleural fluid, any recovered by these maneuvers usually can be assumed to be the offending agent. Cold agglutinin determinations, complement fixation tests, and acute and convalescent viral antibody titers should be obtained when indicated.

## BACTERIAL PNEUMONIAS

In the 1940's the pneumococcus was responsible for 98 per cent of all bacterial pneumonias. Currently, it is losing some ground to gram-negative bacilli and other opportunistic pathogens,<sup>6, 19, 20</sup> but it is still the most frequently encountered agent in bacterial pneumonias acquired outside the hospital setting. Although many patients describe an antecedent upper respiratory tract infection, prospective virologic studies have failed to implicate viral infections other than influenza and measles as triggering events in the development of bacterial pneumonia.<sup>2, 9, 13, 20</sup>

**Table 3.** *Bacterial Agents Responsible for Pneumonias Acquired Outside the Hospital*

COMMON	UNCOMMON	RARE
D. pneumoniae	Hemophilus influenzae Klebsiella pneumoniae Staphylococcus aureus	Bacillus anthracis Bacteroides sp. B. pertussis Brucella sp. Enterobacter sp. E. coli Francisella tularensis Malleomyces mallei
		Malleomyces pseudomallei M. tuberculosis Neisseria meningitidis Nocardia sp. Proteus sp. Pseudomonas sp. Salmonella sp. Streptococcus pyogenes Yersinia pestis

The classic picture of lobar pneumococcal pneumonia usually occurs during the winter and typically begins in explosive fashion in a middle-aged patient. Frequently, the first definitive symptom is a single teeth-chattering chill lasting 30 minutes or longer.\* This is followed quickly by fever and cough, initially productive of small amounts of blood-streaked or rusty (degraded hemoglobin) sputum. Nearly three fourths of the patients will develop sharp pleuritic chest pain which often is severe enough to evoke a grunt of pain with each breath. The patient generally presents to the physician in a toxic state. Examination of the chest reveals dullness to percussion, bronchial breath sounds, increased fremitus, and fine, crepitant rales over the involved area. A peripheral blood smear often reveals a brisk leukocytosis (over 10,000 white cells) with a shift to the left. The chest x-ray film usually exhibits evidence of an infiltrate corresponding to the area of the abnormal physical findings.

Gram stain of the sputum will reveal many granulocytes and gram-positive diplococci in pairs and short chains. Blood culture will be positive for pneumococci in 20 to 30 per cent of the cases, but the frequency of positive blood cultures is increased by obtaining more of them earlier in the course of the disease.

The above description is that of a typical case of lobar pneumococcal pneumonia, and treatment with modest doses of penicillin will usually result in a rapid fall in temperature and the cure of the patient. Unfortunately, not every patient with pneumococcal pneumonia will present with this classical picture. Currently, a more common presentation of pneumococcal pneumonia takes the form of a subtle bronchopneumonia, both clinically and roentgenographically, making differentiation from other pneumonias difficult. Some of the other bacteria that need to be considered in the differential diagnosis are listed in Table 3.

Staphylococcal pneumonia is an acute, rapidly progressive disease that frequently ends in death if appropriate therapy is delayed. This type of pneumonia is more commonly acquired in hospitalized patients, but may be contracted in the community by infants, the elderly, or otherwise debilitated individuals, especially in patients recently discharged from a

\*In the absence of salicylate therapy or pneumococcal complications, recurrent shaking chills should suggest a pulmonary pathogen other than the pneumococcus.

hospital or persons living with them. Following an epidemic of viral influenza, staphylococcal pneumonia may attack any age group.<sup>11, 12, 14</sup> Abscess formation, rare in pneumococcal pneumonia, is seen frequently in staphylococcal pneumonia and pneumatocele formation is considered by many to be a pathognomonic finding.

Klebsiella pneumonia is another uncommon cause of bacterial pneumonia which must be differentiated from pneumococcal pneumonia. It should be specifically suspected in alcoholics, especially in the summer, but it is important to emphasize that most pneumonias in alcoholics are pneumococcal.<sup>5</sup> Klebsiella also tends to infect elderly patients or those with underlying bronchopulmonary disease.<sup>17</sup> As with all gram-negative bacillary pneumonias, the disease is rapidly progressive. The sputum is not as characteristic as was once taught, and the classically described pink, sticky, and jelly-like material also may be seen in pneumococcal pneumonia caused by Types III and VIII, mucoid strains with a thick polysaccharide capsule. Conversely, the sputum in Klebsiella pneumonia may be loose and thin. Gram stain usually reveals rather plump encapsulated gram-negative rods in association with granulocytes. It is crucial to recognize this form of pneumonia because the mortality rate is very high if incorrectly treated.

*Hemophilus influenzae* causes pneumonia primarily in children under 3 years of age, but recently has been reported more frequently in older children and adults.<sup>8, 21</sup> It should be suspected in patients with underlying pulmonary disorders such as cystic fibrosis, chronic bronchitis, and chronic obstructive lung disease. A reasonable explanation for the increasing frequency of this type of pneumonia is that prior to the antibiotic era, most children had acquired protective antibody by 10 years of age. With the introduction of antibiotics, and their widespread use, fewer children and adults have had the infectious experience required to develop immunity to *Hemophilus influenzae*. It is important to consider the possibility of *H. influenzae* pneumonia among adults because the organism is resistant to ordinary doses of penicillin G.

When a patient fails to respond to treatment it is important to consider unusual pathogens (Table 3) and to search for complications (Table 4). The first step is to re-examine the patient, to repeat examination of the sputum by microscopy and culture, and to obtain further blood cultures, chest x-ray films and other appropriate diagnostic tests. It is important to

**Table 4.** *Some Pulmonary and Extrapulmonary Complications of Bacterial Pneumonia*

PULMONARY	EXTRAPULMONARY
Sterile pleural effusion	Meningitis
Empyema	Brain abscess
Lung abscess	Endocarditis
Bronchiectasis	Pericarditis
Pulmonary fibrosis	Arthritis
Slow resolution	Osteomyelitis

recognize that penicillin and other antibiotics routinely alter the normal upper respiratory tract flora. Changing antibiotic therapy simply because subsequent sputum cultures yield resistant organisms is unnecessary and often harmful. An appropriate change in antimicrobial treatment should be considered only if the sputum becomes more purulent, the findings on x-ray examination worsen, and the patient deteriorates in terms of increasing fever, chills, or respiratory distress.

## NONBACTERIAL PNEUMONIAS

One of the most common nonbacterial pneumonias encountered is caused by *Mycoplasma pneumoniae*. This agent truly stands by itself because it is neither a bacterium nor a virus. It lacks a rigid cell wall, but is susceptible to certain antibiotics. This disease occurs most commonly in children and young adults and may appear at any time of the year. Family outbreaks have been described. Pneumonia caused by this agent is less common in persons under age five or over age twenty-five, but it may occur in any age group.<sup>1</sup> The onset is quite gradual and the major symptoms are a severe headache, a hacking irritating cough productive of scanty, mucoid sputum, anorexia, malaise, and low-grade fever.

Physical examination reveals a mild to moderately ill patient with signs of an upper respiratory tract infection. The tympanic membranes should be examined since the presence of bullous myringitis, although uncommon, strongly supports the diagnosis of *Mycoplasma pneumoniae* infection.<sup>3</sup> Examination of the chest usually fails to reveal signs of consolidation, although fine rales are frequently heard. Chest x-ray examination characteristically reveals more extensive involvement than would have been predicted by physical examination, and often there are patchy linear or hazy infiltrations primarily in the lower lobes. Rarely, lobar consolidation may occur, making radiologic differentiation from pneumococcal pneumonia extremely difficult, if not impossible.

The peripheral leukocyte count and differential count are usually normal. Testing for cold agglutinin antibody titer is recommended for all pneumonia cases, and if the titer rise is four-fold or greater, the diagnosis of *M. pneumoniae* infection is highly suspect. Single titers of 1:64 or higher are quite suggestive,<sup>10</sup> but this may vary from laboratory to laboratory. The titer of cold agglutinins has been reported to rise in proportion to the degree of lung involvement, but elevated titers may be seen even in mild cases. The cold agglutinin antibody is a nonspecific response, and may be found in a variety of viral illnesses including influenza. The more specific and confirmatory test is complement fixation determination of antibody to the specific antigen of *M. pneumoniae*, and this should always be done in conjunction with the cold agglutinin determination.

A variety of true viruses are capable of causing pneumonia in both children and adults (Table 5).<sup>5, 6, 9, 13, 19</sup> Clinically, there is little to distinguish one virus from another, but presumptive diagnoses are sometimes possible when dealing with a confirmed outbreak of influenza or adenovirus disease in the community, or if an exanthem due to measles or varicella-zoster virus is present. Lung involvement with viral agents

**Table 5.** *Viruses Capable of Producing Pneumonias in Children and Adults\**

	CHILDREN	ADULTS
Influenza A + B	+	+
Parainfluenza (1-4)	+	Rare
Respiratory syncytial virus	+	Rare
Adenovirus	+	+ <sup>§</sup>
Measles	+	+
Varicella	—	+
Cytomegalovirus	—	+

\*+ = occurs occasionally; — = occurs rarely, if at all.

§§ most likely to occur in closed populations, especially the military

produces a spectrum of disease ranging from subclinical infection to severe pneumonia and death.<sup>15</sup> Unfortunately, there is nothing characteristic among these many viral pneumonias either in the physical examination or in the laboratory findings, and the specific diagnosis can be confirmed only retrospectively either by the isolation of the virus or by the observation of a four-fold or greater rise in serum antibody titer to the specific agent.

An even less common group of nonbacterial pneumonias which occasionally mimic pneumococcal pneumonia are those due to rickettsiae or chlamydiae. Q fever pneumonia (caused by *Coxiella burnetii*) is seen in persons exposed to infected cattle, goats, and sheep, and in laboratory personnel who work with the organism. Chlamydial disease is represented by psittacosis pneumonia in persons who are exposed to infected birds—pet shop employees, pigeon handlers, poultry workers, and those who keep parrots or parakeets as pets. In addition, fungal pneumonias must be considered in patients with appropriate epidemiologic histories—*Histoplasma capsulatum* in a patient from an endemic area or with a heavy exposure to contaminated dust or soil (e.g., cleaning chicken coops; visiting bat-infested caves); *Coccidioides immitis* in a patient who has recently visited the endemic area in the southwestern United States; and *Sporotrichum schenkii* in a greenhouse worker or someone exposed to the contaminated dusts of Sphagnum peat moss.

Finally, one could be confronted with a protozoan pneumonia caused by *Pneumocystis carinii*,<sup>18</sup> an organism that invades the lungs of patients who have a suppressed immune system as a result of leukemia or lymphoma, or following immunosuppressive therapy for cancer, a collagen disease, or organ transplantation. The onset of this type of pneumonia is usually insidious; the disease is slowly progressive and in its earliest stages most resembles a viral pneumonia. It is characterized by increasing dyspnea and bilateral ill-defined and hazy pulmonary infiltration on x-ray examination. It is frequently associated with concurrent infection by viruses (cytomegalovirus), bacteria, and fungi such as *Aspergillus* species. Diagnosis is most reliably achieved by means of a lung biopsy.

## GENERAL THERAPEUTIC APPROACH

The management of a patient with pneumonia requires certain supportive maneuvers. Restricted activity and a light diet rich in fluids help maintain adequate nutrition and hydration. Frequently, intravenous fluids are necessary in the acutely ill patient. Arterial blood gases should be analyzed in patients with underlying cardiac or pulmonary disease, severe dyspnea, or cyanosis, and humidified oxygen administered when indicated. Suppression of cough and pleural pain should be considered for patients who are obviously becoming fatigued, but this must be approached with caution and the patient observed closely for decreasing respiratory rate or hypoxia. Control of excessive fever is indicated in patients with severe heart disease to prevent the onset or worsening of congestive heart failure or acute coronary insufficiency.

Insufficient attention has been given to the management of excessive respiratory secretions and pulmonary toilet in patients with pneumonia. Slow resolution of an otherwise uncomplicated pneumonia may be due in part to this oversight. The concept of drainage is one of the cornerstones in the treatment of any infection and should not be overlooked in pulmonary infections. Attempts to improve drainage and control secretions should include frequent intermittent positive pressure breathing coupled with supervised postural drainage and chest wall clapping. Expectorants may also be of value.

## SPECIFIC ANTIMICROBIAL THERAPY

The essential first step in treating pneumonia is to decide whether or not an antimicrobial drug is needed. Therapy should be directed to specific organisms. The use of broad-spectrum antibiotics in the hope of "covering" multiple pathogens is seldom necessary since most pneumonias in this group are nonbacterial. The "shotgun" approach to treatment may lead to superinfections with resistant organisms such as staphylococci and pseudomonas. However, in certain situations, potent antibiotics are indicated. For instance, semisynthetic penicillins or cephalosporins should be used to treat presumed bacterial pneumonia during an influenza epidemic until staphylococcal infection is safely excluded. Ampicillin may be used in a patient with presumed bacterial pneumonia or bronchitis superimposed upon bronchiectasis or other chronic pulmonary diseases until *H. influenzae* infection is ruled out.

Table 6 lists the drugs of choice and some of the alternative agents for treatment of pneumonias acquired outside the hospital. Penicillin remains the drug of choice for most patients, and for uncomplicated pneumococcal pneumonia, it should be given in relatively small doses, such as 600,000 units of procaine penicillin administered intramuscularly every 12 hours or 500,000 units of aqueous crystalline penicillin administered intravenously every 4 hours; larger doses are not necessary even if the blood culture is positive because the organism is so exquisitely susceptible to penicillins. Furthermore, larger doses increase the

Table 6. Selection of Antibiotics for Treatment of Pneumonias

INFECTING AGENT	ANTIBIOTIC OF CHOICE (alternative antibiotic)
Pneumococcus	Penicillin G (erythromycin, clindamycin)
Staphylococcus aureus	Semisynthetic penicillinase-resistant penicillin (cephalothin, clindamycin)
Klebsiella pneumonia	Cephalothin (chloramphenicol) plus kanamycin (gentamicin)
Hemophilus influenzae	Ampicillin (tetracycline, chloramphenicol)
Enterobacteria and Pseudomonas*	Gentamicin; until susceptibility tests completed*
Streptococcus pyogenes	Penicillin (clindamycin, erythromycin)
Mycoplasma pneumonia	Tetracycline (erythromycin)
Viral	None; no prophylaxis indicated
Unknown, probably bacterial	Penicillin
Rickettsial	Tetracycline (chloramphenicol)
Chlamydial	Tetracycline (chloramphenicol)
Pneumocystis carinii	Pentamidine isethionate, pyrimethamine and sulfadiazine
Tbc, Fungal	Appropriate

\*Least toxic alternative agent should be employed when pathogen is susceptible (e.g., ampicillin, cephalosporins, carbenicillin, etc.)

risk of superinfections and do *not* increase the rate at which a patient recovers; they are indicated only in the presence of extrapulmonary complications. Oral penicillin should not be used initially in acutely ill patients because absorption may be unpredictable. However, the route of administration may be changed when the clinical situation permits. Doses of many of the antimicrobial drugs effective against other pulmonary pathogens listed in Table 6 are discussed in other papers in this symposium.

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## Hospital-Acquired Pneumonia

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Pneumonia continues to be a serious problem despite the availability of numerous potent antimicrobial drugs.<sup>36</sup> It now appears to be the fifth most common cause of death in the United States.<sup>53</sup> From 9 to 10 per cent of the annual admissions of some large community hospitals have been for treatment of pneumonia.<sup>71, 73</sup> In more than 15 per cent of patients admitted for treatment of pneumonia, bronchopulmonary superinfections develop and often cause death.<sup>73</sup> Data are now available indicating that pneumonia is acquired after admission in from 0.5 to 5 per cent of all hospitalized patients.<sup>66</sup> Furthermore, more than two thirds of deaths attributed to hospital-acquired infections on some medical services have been caused by pneumonia.<sup>54</sup>

Organisms identified as causing pneumonia appear to be considerably different for the group of patients whose infection is acquired within the hospital than for the group of patients whose pulmonary infection is contracted in the community.<sup>12</sup> Although there is some overlapping of etiologic agents, pneumonia developing in hospitalized patients is more likely to be caused by gram-negative bacilli, staphylococci, or unusual opportunistic pathogens. The hospital provides a reservoir for some of these organisms. Often the pathogenesis of pneumonia may be related directly or indirectly to underlying diseases of the patients or to various forms of therapy administered in the hospital. Frequently, the presenting manifestations of hospital-acquired pneumonia are subtle and insidious; they may be unrecognized, overlooked or mistaken for the expressions of

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Figure 1. Roentgenogram of the chest in a patient with bacteremic *Pseudomonas* pneumonia secondary to aspiration. Diffuse alveolar infiltrate in right lung.

other illnesses. Therapy is often complicated by resistance of the causative organism to all but the most toxic drugs. This presentation will be concerned with selected aspects of hospital-acquired (nosocomial) pneumonia.

### PNEUMONIA CAUSED BY GRAM-NEGATIVE BACILLI

Enteric gram-negative bacilli and *Pseudomonas* now appear to be the most common causes of pneumonia acquired in the hospital.<sup>66</sup> Results of recent studies<sup>32, 33, 70</sup> have shown that these organisms become prevalent in the oropharyngeal flora of hospitalized patients who have serious illnesses. This may occur quite rapidly after admission and does not appear to be explained entirely by administration of antimicrobial drugs or by inhalation therapy. Since most bacterial pneumonias begin with inhalation or aspiration into the lung of organisms present in the upper respiratory tract, this alteration in the pharyngeal flora of seriously ill patients may be an important first step in the pathogenesis of hospital-acquired pneumonia caused by gram-negative bacilli.<sup>32</sup>

Massive aspiration of gastric contents into the lung is often a catastrophic event associated with retching, vomiting, cough, dyspnea, and cyanosis.<sup>59</sup> However, aspiration of lesser amounts of gastric contents or of oropharyngeal secretions is often occult and goes unrecognized. This is particularly true in comatose, obtunded, or debilitated patients who have impaired cough and gag reflexes. The findings of studies now

available indicate that aspiration of oropharyngeal secretions or gastrointestinal contents into the lungs occurs frequently in hospitalized patients and is a common cause of death.<sup>2, 9, 28, 47</sup> Figure 1 shows the chest x-ray film of a patient who had granulocytopenia secondary to therapy for pemphigus; fatal *Pseudomonas* pneumonia with bacteremia developed after a documented episode of aspiration. It seems likely that most cases of gram-negative bacillary pneumonia are caused by unrecognized aspiration. Utilization of appropriate measures<sup>2</sup> to prevent aspiration in hospitalized patients may help to decrease the incidence of pneumonia due to those organisms.

Evidence provided by recent studies indicate that inhalation therapy equipment which incorporates reservoir nebulization frequently becomes contaminated with gram-negative bacilli and generates aerosols containing large numbers of these organisms.<sup>15, 57, 67</sup> These bacterial aerosols are of a particle size capable of reaching the alveoli. In contrast to nebulizers, humidifiers merely saturate gas with water and do not ordinarily generate bacterial aerosols. The source of the bacterial aerosols in intermittent-positive-pressure breathing equipment appears to be the reservoir nebulizer jet, which is not decontaminated by standard cleansing techniques.<sup>57</sup> The contaminated jet serves as a reservoir to repeatedly inoculate reservoir fluid with viable gram-negative bacilli.

Evidence that bacterial aerosols generated by inhalation therapy equipment can cause pneumonia has come from several sources. Pierce and associates<sup>52</sup> were able to reduce considerably the incidence of necrotizing pneumonia at the Parkland Memorial Hospital in Dallas, Texas, by routine daily decontamination of reservoir nebulizers with 0.25 per cent acetic acid. Several investigators<sup>1, 7, 24, 44, 50, 60, 65</sup> have reported epidemics of gram-negative bacillary infections of the respiratory tract which were clearly related to contaminated respiratory therapy equipment. As a result of these observations, sensible recommendations are now available for decontamination of respiratory therapy equipment.<sup>6, 10, 51</sup>

Tracheostomy is recognized as being another important factor in the pathogenesis of hospital-acquired pneumonia.<sup>23, 27, 39, 63, 72</sup> The organisms most frequently causing pneumonia after tracheostomy are *Pseudomonas aeruginosa*, enteric gram-negative bacilli, and *Staphylococcus aureus*. These organisms may be acquired from the patient's own indigenous flora or from the hospital environment. There are many possible sources of infection and modes of transmission of gram-negative bacilli in the hospital environment. These organisms may be on the hands of nurses and other hospital personnel, in food, in water, and in a wide variety of solutions and medications.

Some of the factors cited as predisposing to pneumonia after tracheostomy include unsterile suction technique, trauma to the trachea and bronchi with suctioning, inspissated or pooled secretions, maintenance of tracheal catheters in solutions contaminated by gram-negative bacilli, contaminated respiratory equipment, prophylactic antibiotic therapy, and aspiration of food, liquids, oral secretions, or gastric contents. Cameron and associates<sup>8</sup> demonstrated evidence of aspiration in a surprisingly high proportion of patients with tracheostomies. For a vivid

description of some of the possible "breaks" in technique of tracheal suctioning, the interested reader is referred to the excellent report of Sutter and her associates.<sup>72</sup>

Recently, Tillotson and Lerner<sup>74-78</sup> described the clinical, laboratory, roentgenographic, and pathologic findings in 82 cases of pneumonia caused by gram-negative bacilli at the Detroit Receiving Hospital. Criteria for diagnosis included: (1) isolation of the same gram-negative bacillus as the only or predominant organism from two or more consecutive specimens of sputum, (2) isolation of the same bacteria from cultures of the blood and sputum in close temporal proximity, or (3) isolation of the organism from the pleural fluid. In addition, the clinical course of the patient had to be compatible with the clinical diagnosis of parenchymal disease of the lung.

Most patients were men (average age, 53 years), and the majority were admitted for treatment of pneumonia; the mortality was almost 50 per cent. Virtually all the patients had serious underlying noninfectious diseases. Included in this category were chronic alcoholism, chronic cardiac or pulmonary diseases, diabetes mellitus, and chronic renal disease.

The most common causative organisms were *Klebsiella-Enterobacter*, *E. coli*, *Pseudomonas*, *Proteus*, and *Bacteroides*. Pneumonia appeared to be caused either by aspiration or by bacteremia from sources of infection in the genitourinary or gastrointestinal tracts. Pneumonias due to *Proteus* and *Klebsiella-Enterobacter* usually were secondary to aspiration. They tended to produce dense lobar consolidations with abscesses; when lesions involved the upper lobes of the lungs, the trachea was often deviated to the side of the lesion.

Other investigators<sup>30, 37, 61</sup> have described roentgenologic features of *Klebsiella* pneumonia, which include bulging interlobar fissures, sharp margins of the advancing border of the pneumonic infiltrate, and early abscess formation. *E. coli* commonly produced patchy bilateral lower lobe infiltrates with early empyemas; these lesions were thought to be caused by bacteremia arising from extrapulmonary sites of infection. *Bacteroides* pneumonias most frequently appeared to be minimal lower lobe bronchopneumonias with large and rapidly accumulating pleural empyemas. In some instances, bacteremia appeared to be the source of the pulmonary lesions due to *Bacteroides*; in others, the pathogenesis was less clear. *Pseudomonas aeruginosa* caused bilateral diffuse lower lobe bronchopneumonias with abscess formation. These pulmonary lesions appeared to be caused by aspiration. Roentgenograms demonstrated distinctive nodular infiltrates in the lower lobes with small areas of radiolucency consistent with microabscesses.

In the last 6 years, there have been a number of additional reports of cases of *Pseudomonas* pneumonia.<sup>18, 31, 38, 40, 49, 58, 64</sup> Granulocytopenia often appears to be a factor predisposing to the complication and limiting the chances for survival.<sup>40, 49</sup> Invasion on the walls of small blood vessels with numerous gram-negative bacilli (Fig. 2) is a characteristic finding, but absence of these lesions does not exclude the diagnosis of *Pseudomonas* pneumonia. Roentgenologic findings may vary considerably among individual patients or at various times in the same patient.<sup>31, 58</sup> The

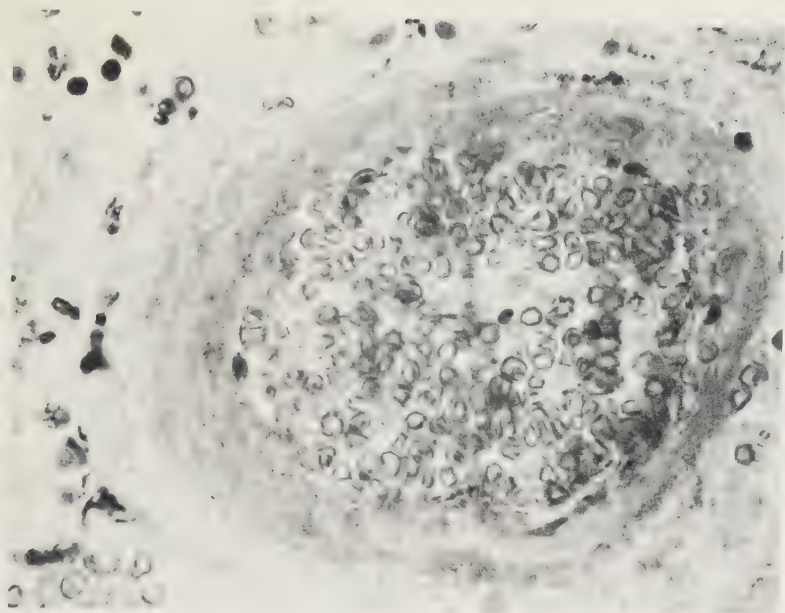


Figure 2. Transmurial involvement of pulmonary blood vessel with a myriad of gram-negative bacilli. Gram stain  $\times 640$ .

basic patterns involve bronchopneumonia, nodular and occasional interstitial patterns, abscess formation, and pleural thickening, empyema, or effusion.<sup>58</sup>

In the last decade, *Serratia marcescens* has become recognized as being an important cause of hospital-acquired infections.<sup>7, 60, 65</sup> Some strains produce a red pigment, prodigiosin, which may cause a reddish discoloration of the sputum and be mistaken for hemoptysis.<sup>20, 62</sup> Recently, Meltz and Grieco<sup>43</sup> described the characteristics of pneumonia caused by *Serratia marcescens*. The hospital-acquired pneumonia developed in elderly patients with cardiac or chronic pulmonary diseases. There were no distinctive signs or symptoms and pseudohemoptysis was not noted. Mild leukocytosis was evident and roentgenograms usually disclosed moderate lobular infiltration of the upper or lower lobes. Metapneumonic pleural effusions were noted in some patients. The absence of cavitory lesions was clinically helpful in distinguishing pneumonia caused by *Serratia marcescens* from pneumonia produced by *Pseudomonas aeruginosa*.

Selwyn and associates<sup>66</sup> at the University of Edinburgh Hospital found that *Hemophilus influenzae* was a common cause of hospital-acquired pneumonia. In contrast, *Hemophilus influenzae* appears to be an uncommon cause of pneumonia in adults in the United States<sup>22, 34</sup> and has not been a frequent cause of hospital-acquired infections of the lower respiratory tract.<sup>66</sup> Occasionally, this organism has produced pneumonia in adult patients with chronic pulmonary disease or immune deficiency states. Figure 3 shows the chest x-ray film of a patient with chronic lym-

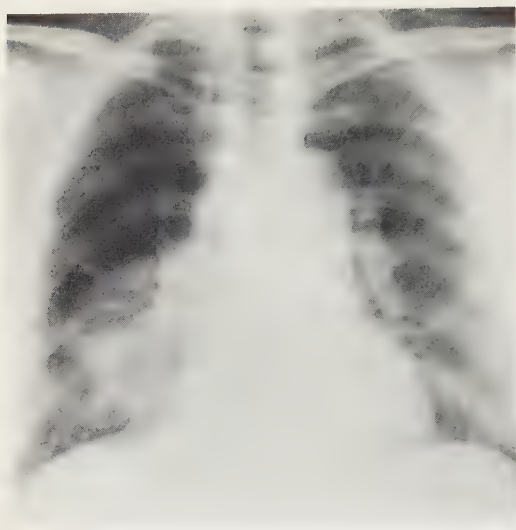


Figure 3. *Hemophilus influenzae* pneumonia which developed in a hospitalized patient.

phatic leukemia and hypogammaglobulinemia who contracted pneumonia due to *Hemophilus influenzae* in our hospital. The diagnosis was based upon recovery of the organism from the blood on three separate occasions at a time when pneumonia was the only site of infection.

One of the more difficult problems with pneumonia due to gram-negative bacilli has been the problem of correct clinical diagnosis. Gram-negative bacilli are often isolated from sputum cultures under circumstances in which their clinical significance is difficult to evaluate—they may be spurious contaminants, harmless commensals, or opportunistic pathogens. Concomitant cultures of blood may be sterile and pleural fluid may not be available for culture. The problem of diagnosis is particularly troublesome in critically ill patients, when several possible causes of fever exist, nonspecific pulmonary infiltrates develop, and cultures of expectorated sputum or tracheal aspirates yield gram-negative bacilli, either in pure growth or with other potential pathogens. Under these circumstances, microscopic examination of a gram-stained smear of freshly collected specimens of sputum or transtracheal aspirates<sup>25</sup> is indispensable. Bacillary infection may be diagnosed when the smears show numerous gram-negative bacilli and an abundance of polymorphonuclear leukocytes, especially when some of the organisms have been ingested by the phagocytes. However, in severely leukopenic patients, significant bacillary infection of the lungs may be present without these characteristic changes in the sputum.

Successful treatment of pneumonia caused by gram-negative bacilli depends upon early diagnosis and prompt institution of appropriate antimicrobial therapy. Table 1 lists the currently preferred antimicrobial drugs for the initial therapy of life-threatening pneumonia caused by those organisms. The clinical pharmacology of these drugs will be given in more detail in other papers in this symposium.

**Table 1.** Preferred Antimicrobial Drugs for Initial Presumptive Therapy of Life-Threatening Pneumonia Caused by Gram-Negative Bacilli\*

PRESUMED OR PROVED ETIOLOGIC ORGANISM	ANTIBACTERIAL DRUG PREFERRED	ALTERNATIVE ANTIBACTERIAL DRUG(S)†
<i>Escherichia coli</i>	Gentamicin	Ampicillin, a cephalosporin
<i>Klebsiella</i> sp.	Gentamicin	A cephalosporin
<i>Enterobacter</i> sp.	Gentamicin	Carbenicillin
<i>Serratia marcescens</i>	Gentamicin	Carbenicillin, chloramphenicol
<i>Proteus mirabilis</i>	Gentamicin	Ampicillin, a cephalosporin
<i>Proteus</i> (P) <i>morganii</i> , P. <i>rettgeri</i> , P. <i>vulgaris</i>	Gentamicin	Carbenicillin
<i>Pseudomonas aeruginosa</i>	Gentamicin and carbenicillin	Tobramycin‡
<i>Bacteroides</i>	Clindamycin	Chloramphenicol
<i>Hemophilus influenzae</i>	Ampicillin	Chloramphenicol

\*Definitive antibacterial therapy is determined subsequently from the results of in vitro susceptibility tests and the patients response to treatment.

†Alternative drugs are employed when the pathogen is susceptible in vitro and the patient's clinical condition warrants.

‡Not yet commercially available.

## STAPHYLOCOCCAL PNEUMONIA

Although *Staphylococcus aureus* causes only about 1 per cent of cases of bacterial pneumonia in the general population,<sup>56</sup> its incidence increases during epidemics of influenza.<sup>42</sup> *Staphylococcus aureus* has been a frequent cause of pneumonia in patients dying in hospitals in the past two decades. For example, some studies have shown that staphylococcal infections were present in the lungs at autopsy in from 6 to 24 per cent of patients who had died in hospitals.<sup>46, 55</sup> Since the introduction and widespread use of the semisynthetic penicillinase-resistant penicillins and cephalosporins, staphylococci have caused nosocomial pneumonia less frequently than gram-negative bacilli.<sup>66</sup> In recent years, methicillin-resistant staphylococci have become a major cause of infection in many parts of Europe and Scandinavia, but thus far have only been a minor problem in the United States.<sup>16, 41</sup>

*Staphylococcus aureus* may normally inhabit the anterior nares, upper respiratory tract, and skin of a sizable number of patients and hospital personnel.<sup>79</sup> Likewise, staphylococci may be cultured from hospital air, hospital laundry and laundry chutes, clothing of patients and their attendants, bedsheets and blankets, soiled bandages,<sup>79</sup> and even from contaminated sphygmomanometers. Airborne transmission of staphylococcal infection may occur, but direct person-to-person contact appears to be the most important mode of transmission of pathogenic staphylococci.<sup>80</sup> Patients or hospital personnel with active staphylococcal infections probably constitute the most dangerous source of nosocomial infections caused by those organisms.

Figure 4 is a graphic representation of the clinical course of a patient who had granulocytopenia secondary to immunosuppressive therapy for

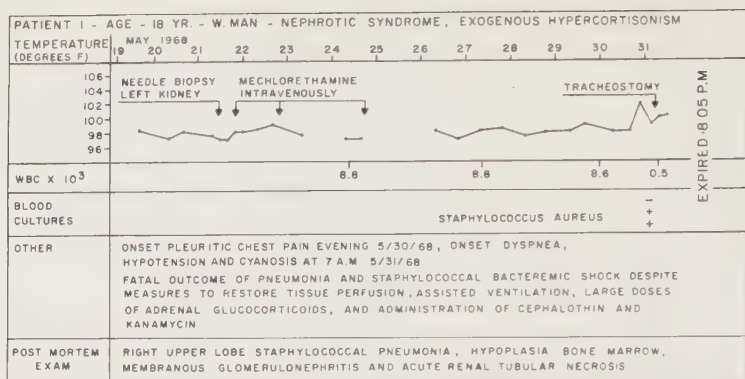


Figure 4. Graphic representation of the clinical course of a patient with fulminating staphylococcal pneumonia.

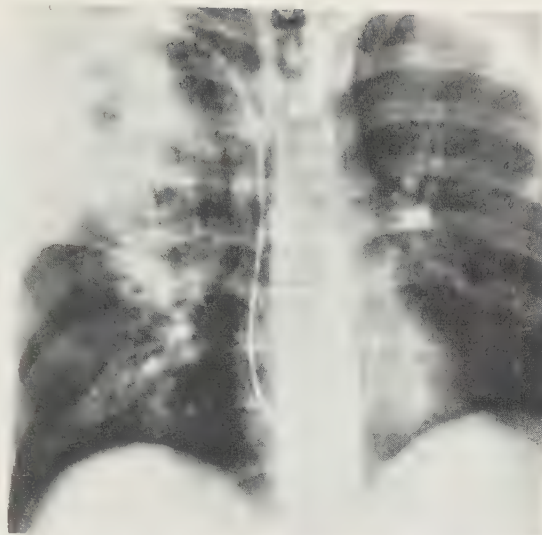
the nephrotic syndrome, and whose roommate in the hospital was discovered to have a staphylococcal infection in the region of an external arteriovenous shunt. As a result of probable cross-infection, fulminating staphylococcal pneumonia and bacteremia developed in the patient with granulocytopenia. The chest x-ray film taken at the onset of the illness (Fig. 5) showed an infiltrate in the upper lobe of the right lung. The chest film taken the following morning showed increase in the size of the infiltrate with areas of rarefaction (Fig. 6). Death occurred rapidly despite appropriate therapy. Clearly, this indicates the potential severity of staphylococcal infection in the patient with compromised resistance to bacterial infection.

Staphylococcal pneumonia tends to occur at the extremes of life—in infants or in elderly patients.<sup>18, 19</sup> Among the major predisposing diseases



Figure 5. Roentgenogram of the chest showing an alveolar infiltrate in the right upper lobe at the onset of staphylococcal pneumonia in patient whose course is shown in Figure 4.

Figure 6. Roentgenogram of the chest in the same case taken approximately 12 hours later. Note the rapid progression of the infiltrate and areas of rarefaction (pneumatoceles).



are chronic pulmonary or cardiac disease, cystic fibrosis, chronic renal failure, diabetes mellitus, chronic liver disease, acute leukemia, and malignant neoplasms. Staphylococcal pneumonia is often a fatal complication of viral influenza.<sup>42</sup> Among the therapies predisposing to staphylococcal pneumonia are administration of "broad-spectrum" antibiotics, antineoplastic drugs, and adrenal glucocorticoids. Staphylococcal pneumonia may also occur as a postoperative complication of various surgical procedures or as a sequel to aspiration.

Staphylococcal pneumonia may arise in the lungs, or it may be a complication of bacteremia from sources of infection elsewhere in the body. Bacteremia appears to be relatively uncommon in primary staphylococcal pneumonia and its occurrence may be a clue to another focus of infection. In the metastatic form of staphylococcal pneumonia, early in the course roentgenograms may show multiple, patchy, round, or oval densities in the periphery of both lungs.<sup>26, 69</sup> These lesions may clear rapidly as others appear in different areas; or they may rapidly go on to cavitation with abscess formation. Figure 7 shows the chest x-ray film of one of our patients who had pulmonary lesions secondary to polymicrobial bacteremia with *Staphylococcus aureus* and *Proteus mirabilis*. Note the cavitating lesion in the lower lobe of the right lung and evidence of spontaneous pneumothorax on the left. The development of spontaneous pneumothorax as a complication of pneumonia is strongly suggestive of staphylococcal disease.<sup>14, 69</sup>

The clinical course of primary staphylococcal pneumonia has been described by several investigators.<sup>5, 11, 14</sup> It varies from a fulminating illness with death in a matter of days to a more chronic illness with abscess formation. Often the pulse will be slow in proportion to the temperature. The sputum may be frankly purulent, hemorrhagic, or have a dirty salmon-pink appearance, resembling anchovy sauce.<sup>5</sup>

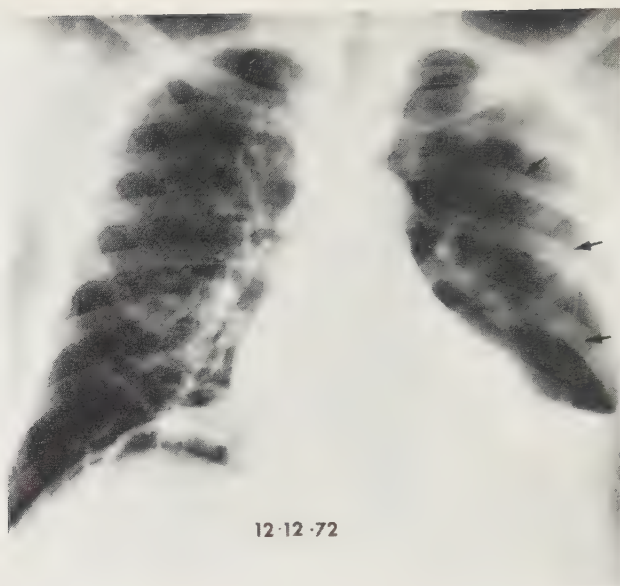


Figure 7. Posteroanterior chest film, showing right lower lobe abscess with fluid level and pneumothorax of the left chest (arrows).



Figure 8. Posteroanterior chest film from patient with staphylococcal pneumonia and empyema.



Figure 9. Lateral view of chest, same patient.

In the early stages, the severity of the patient's illness may be out of proportion to the degree of changes in the chest film.<sup>14</sup> The earliest chest x-ray findings consist of patchy areas of opacification which may be scattered in multiple lobes or may be confined to one lobe. Frequently the changes are bilateral or involve multiple lobes on one side. The lesions rapidly progress to cavitation and abscess formation (Figs. 8 to 10); pleural effusion or empyema is common and may be massive.

Thin-walled cysts or pneumatoceles, which often give a typical soap-bubble appearance<sup>5</sup> on the chest x-ray film (Fig. 10), are strongly suggestive of staphylococcal pneumonia.<sup>5, 14, 69</sup> The pneumatocele develops as a result of perforation of an abscess into a bronchial wall, thus permitting air to enter the cavity.<sup>13</sup> The pneumatoceles are inflated by a check-valve action of the edematous bronchial mucosa or by luminal secretions. These lesions usually appear within the first week of the pneumonia and usually disappear in an average of 6 weeks; surgery is rarely indicated. Pneumatoceles are said to occur more commonly in children than in adults with staphylococcal pneumonia.<sup>69</sup>

Since *Staphylococcus aureus* may be a normal inhabitant of the upper respiratory tract in some patients,<sup>19</sup> mere demonstration of the organism in a sputum specimen contaminated by oropharyngeal secretions is insufficient evidence of infection of the lungs or bronchi. Trans-tracheal aspiration of sputum may be helpful in diagnosing staphylococcal pneumonia when expectorated sputum contains large



Figure 10. Lateral chest x-ray after injection of contrast media into chest tube. Note the typical "soap-bubble" appearance of the pneumatoceles.

numbers of staphylococci.<sup>25</sup> In staphylococcal pneumonia, smears of the sputum will usually show innumerable gram-positive cocci in clumps and many polymorphonuclear leukocytes. Some of the cocci may be located intracellularly as a result of phagocytosis by the leukocytes.

Penicillin G is the drug of choice for treatment of pneumonia caused by nonpenicillinase-producing staphylococci. Methicillin, oxacillin, nafcillin, or cephalothin is useful for treatment of pneumonia caused by penicillinase-producing staphylococci. Lincomycin or clindamycin may be useful if the organism is susceptible and the patient is unable to tolerate penicillins and cephalosporins. Vancomycin appears to be the drug of first choice for treatment of pneumonia caused by methicillin-resistant staphylococci.<sup>41</sup>

### **PULMONARY INFECTIONS COMPLICATING IMMUNOSUPPRESSIVE THERAPY**

A wide variety of pulmonary infections may develop in hospitalized patients who are being treated with cytotoxic and immunosuppressive drugs for carcinoma, malignant lymphoma, leukemia, collagen vascular diseases, or serious cutaneous diseases, or in recipients of organ transplants.<sup>29</sup> In addition to aerobic and anaerobic gram-negative bacilli<sup>4</sup> and staphylococci, pulmonary lesions may be caused by nocardia,<sup>48</sup> various fungi including aspergillus<sup>41</sup> and *Candida*, viruses, including the cyto-

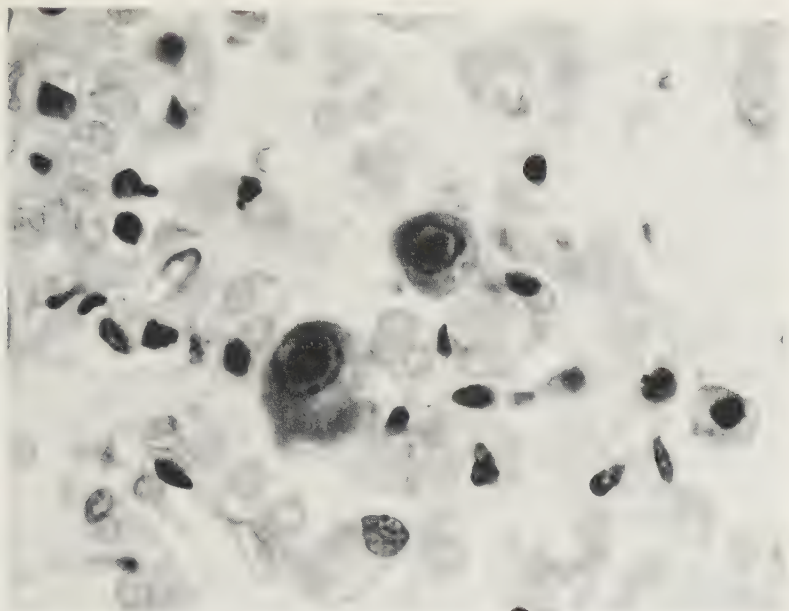


Figure 11. Section of lung from renal transplant recipient showing two intra-alveolar cytomegalic cells with large intranuclear inclusion bodies separated from the nuclear membrane by a clear zone. Hematoxylin and eosin stain,  $\times 819$ .



Figure 12. Section from lung of patient with chronic lymphatic leukemia showing an aggregate of cysts of *Pneumocystis carinii*. Toluidine blue stain,  $\times 820$ .

megalovirus (Fig. 11), *Pneumocystis carinii* (Fig. 12) and other agents. It is not always clear whether these are hospital-acquired infections or are merely a reactivation of a latent infection.

Often cultures and smears of sputum or transtracheal aspirates are not diagnostic and administration of a wide variety of antimicrobial drugs fails to control the infection. Under these circumstances, bronchial brush biopsy, transthoracic needle aspiration, or open lung biopsy and culture may be of extreme value in establishing a diagnosis and instituting specific therapy. Often there is considerable delay and vacillation before decisions are made to perform such procedures, and valuable time is lost. It is important, therefore, to consider these procedures early in the patient's illness before the infection becomes irreversible. A number of reports now are available demonstrating the value and relative safety of such methods in the etiologic diagnosis of pulmonary infections in adults and children.<sup>3, 21, 35, 45</sup>

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## Bacterial Meningitis

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Florid descriptions of the brains of individuals dying from purulent meningitis date back to ancient times. In the preantimicrobial era the mortality rate of bacterial meningitis exceeded 90 per cent, and most survivors were neurologically devastated. With the availability of effective antibiotic therapy the mortality was reduced to a range of 10 to 20 per cent, where it has remained essentially unchanged during the past 10 to 15 years. This significant mortality rate, together with the occurrence of serious neurological sequelae in a number of survivors, underscores the continuing challenge of bacterial meningitis.

### EPIDEMIOLOGY

The incidence of bacterial meningitis has remained nearly the same over the past 40 years, affecting approximately 5 individuals per 100,000 population.<sup>30, 29</sup> The majority of these are children less than 15 years of age, accounting for approximately 25,000 cases per year in this country. Of these, about 2200 die; conservatively estimated, about 4000 to 5000 have significant residual complications.

Bacterial meningitis tends to have its highest incidence in the winter, but occurs throughout the year. There is no recognized racial predilection, and the sex difference is not remarkable, although some studies reveal a preponderance of males over females. These latter reports show a male-to-female ratio of approximately 3 to 2, which is a considerably lower male-to-female ratio than that seen in the majority of infectious diseases.<sup>31</sup> The incidence of bacterial meningitis is age-related; approximately 15 per cent of cases occur under 1 month of age, 37 per cent before 1 year of age, and 75 per cent before 15 years of age.<sup>31</sup> In reality, then, this is primarily a pediatric disease. Mortality also varies with age, being highest in the first year of life, decreasing during the middle years and rising again after the age of 50 to 60 years. The mortality is significantly higher in males than in females and in non-whites than in Cauca-

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sians. The latter has been attributed by some to differences in the socioeconomic status of the two groups.

A number of factors predispose individuals to bacterial meningitis. These include respiratory infection and otitis media, mastoiditis, head trauma, recent neurosurgical procedures, sickle cell anemia, and agammaglobulinemia.

## ETIOLOGY

The bacterial agents causing meningitis differ considerably, depending upon the age of the patient. In the newborn infant, gram-negative bacilli, *Staphylococcus aureus*, and Lancefield Group B streptococci predominate. In children beyond the neonatal stage, *Hemophilus influenzae*, in particular, but also *Neisseria meningitidis* and *Diplococcus pneumoniae* are the most common etiologic agents; the latter two organisms predominate in adults. These three organisms account for approximately 65 to 70 per cent of all cases of bacterial meningitis in children and adults. In adults over 50 years of age, the pneumococcus is the most common cause of bacterial meningitis acquired outside the hospital. *Listeria monocytogenes*, usually an opportunistic pathogen, has been recognized more frequently in some centers as a cause of meningitis in adults.

*Neisseria meningitidis* is a gram-negative kidney-bean shaped diplococcus which has a tendency to occur intracellularly in polymorphonuclear leukocytes. This organism accounts for approximately 20 to 30 per cent of all cases of bacterial meningitis acquired outside the hospital. Patients of any age may be affected, but the child or young adult is most commonly infected. Meningococcal meningitis has a propensity to occur in epidemics and before 1963 most cases were caused by Group A strains with only sporadic cases caused by strains belonging to Groups B and C. In recent years, however, Group A organisms have accounted for less than 5 per cent of meningococcal isolates. Group B and, more recently, Group C organisms are the predominant serotypes associated with severe clinical disease.

Concomitant with the observed changes in distribution of serotypes has been a marked increase in prevalence of sulfonamide-resistant strains. At least 50 per cent of Group B isolates and up to 90 per cent of Group C strains are resistant to 1.0 mg. per 100 ml. of sulfadiazine. Although Group A organisms have been responsible for a relatively small number of illnesses, there is evidence that this serotype has also become resistant to sulfonamide drugs.

The occurrence of petechiae or purpura in approximately 50 to 60 per cent of cases of meningococcal meningitis is very helpful in suggesting a clinical diagnosis. Patients should be examined carefully for evidence of these skin manifestations prior to performing procedures, such as lumbar punctures, which may result in petechiae secondary to trauma. Petechial or purpuric lesions occasionally develop in patients with infections with other bacteria such as Group A streptococci or *Hemophilus influenzae*, as well as with certain viral infections.

Immunity to meningococcal disease correlates with the presence of

circulating bactericidal antibody which, in the natural course of events, probably develops secondary to intermittent nasopharyngeal carriage of various strains of the meningococcus.<sup>21, 42</sup> Vaccines prepared from purified meningococcal polysaccharides are nontoxic and appear to be effective immunizing agents.<sup>3, 22</sup> Further evaluation of these killed vaccines is currently in progress.

*Diplococcus pneumoniae* is a gram-positive diplococcus which is lancet-shaped and exhibits a positive Quellung reaction or capsular swelling when the organism is exposed to specific antibody. This bacterium accounts for 20 to 30 per cent of the total cases other than hospital-acquired bacterial meningitis. Patients of any age may be affected, but the incidence of pneumococcal meningitis is highest at the extremes of life. Approximately two thirds of patients with pneumococcal meningitis have parameningeal foci of infection or pneumonia. This organism is the most common bacterium found in patients with recurrent bacterial meningitis, most of whom have a history of recent or remote head trauma and a known or suspected dural defect.<sup>27, 34</sup> Of 155 patients with pneumococcal meningitis in one series, 11 per cent had more than one episode of bacterial meningitis.<sup>34</sup> In contrast, of 918 patients who had bacterial meningitis caused by other organisms in this same study, only 0.5 per cent had recurrences. Thirty-five per cent of patients with recurrent pneumococcal meningitis had a history of significant head injury, while only 9 per cent of those with nonrecurrent pneumococcal meningitis had a similar history. The pneumococcus also has an apparent predilection for causing meningitis in patients with sickle cell disease, in whom the risk of this infection is estimated to be 500 times greater than that of the general population.<sup>5, 43</sup> Recent evidence indicates that serum from patients with sickle cell disease is deficient in opsonins for the pneumococcus.<sup>30, 53</sup>

*Hemophilus influenzae* is a pleomorphic gram-negative rod, whose shape varies from a coccobacillary form to a long curved rod. The organisms exhibit a positive Quellung reaction with specific antisera, and nearly all cases of *Hemophilus influenzae* meningitis are caused by organisms containing the Type b capsular polysaccharide. This organism is the most common cause of bacterial meningitis in children, peaking between the ages of three months and three years. *Hemophilus influenzae* rarely causes meningitis in adolescents or adults. Indeed, if this type of meningitis occurs in a patient over 10 years of age, one should suspect a parameningeal focus of infection or an immunoglobulin deficiency. The capsular polysaccharide, polyribophosphate, of *H. influenzae* is probably critical to the invasive potential of this organism. A polyribophosphate vaccine has given promising results in toxicity and immunogenicity studies, but a field trial has not yet been undertaken.<sup>2, 47</sup>

Many other organisms may cause bacterial meningitis with perhaps the most important ones being the streptococci, *Staphylococcus aureus*, *Listeria monocytogenes*, and a scattering of gram-negative bacilli. When meningitis develops in a hospital setting in patients with chronic systemic diseases, *Staphylococcus aureus*, *Pseudomonas*, and enteric gram-negative bacilli are more frequently involved. Infections have been reported with more than one organism;<sup>49</sup> but mixed infections are very

rare, particularly if the slides and reagents used for staining are free of bacterial contamination. At least 10 to 15 per cent of cases of purulent meningitis are of unknown etiology. In a sizable proportion of these cases the diagnosis is unknown because patients have been treated with antibiotics before cultures of blood and cerebrospinal fluid were taken.

## CLINICAL FEATURES

The fully developed case of bacterial meningitis usually presents no diagnostic problem. Nuchal rigidity, opisthotonus, bulging fontanel, coma, and convulsions are readily recognized as commonly associated with meningitis. The crucial issue, however, is early diagnosis. Less specific signs and symptoms reported in nearly all large series include the following: fever, anorexia, irritability, vomiting, headache, and lethargy. Convulsions occur in up to one third of patients. It is essential to recognize the clinical manifestations of meningitis early, perform lumbar puncture without delay, and institute appropriate therapy before irreversible brain damage occurs. Indeed, it is axiomatic that whenever a competent observer raises the question of meningitis for whatever reason, lumbar puncture is obligatory. Experienced physicians have estimated that at least 10 negative lumbar punctures for meningitis should be performed for every positive one. Obviously it is not meaningful to attach specific numbers to estimates of this type. However, if all the lumbar punctures which one performs for bacterial meningitis are positive, it is probable that other cases are being missed.

Although considerable overlap may occur, the course of bacterial meningitis tends to fall into two broad categories.<sup>9</sup> The first type is a fulminant disease which develops over a period of approximately 24 hours and is very rapidly fatal. The second type develops more insidiously and progresses more slowly over a period of several days; the prognosis in this form is much more favorable than that in the first type.

Several diseases should be considered in the differential diagnosis of bacterial meningitis. Other forms of meningitis may present in a similar manner. The most common of these is aseptic meningitis caused by a variety of viral agents, but one should be continually suspicious of tuberculous meningitis. In many areas tuberculous meningitis occurs so infrequently that physicians may not become suspicious, and diagnosis is delayed or missed. Pneumonias, primarily of the right upper lobe, may present with meningismus. Shigellosis, primarily in the younger age group, may also present with nuchal rigidity as the predominant symptom; the patient may arrive for examination before he has developed the diarrhea which is characteristically associated with this disease. Renal infections and the acute abdomen may also masquerade under the guise of bacterial meningitis. Local infections of the neck and pharynx such as cervical adenitis, retropharyngeal or peritonsillar abscess may also cause fever and nuchal rigidity which may be mistaken for meningitis. In addition, brain abscess and subdural empyemas may be confused with meningitis. In infants with open cranial sutures, a bulging fontanel may be commonly associated with administration of tetracycline drugs or rarely with hypervitaminosis A or steroid therapy.

## LABORATORY DIAGNOSIS

The most important abnormal laboratory findings in bacterial meningitis are in the cerebrospinal fluid. The fluid may be grossly cloudy, with cell counts totaling hundreds to thousands. The differential cell count in bacterial meningitis almost invariably includes a preponderance of polymorphonuclear leukocytes, but early in the course of viral or tuberculous meningitis, this cell type may also predominate. The cerebral spinal fluid sugar is usually low in bacterial meningitis, often less than 40 mg. per 100 ml. One should always draw a simultaneous blood sugar, and the cerebrospinal fluid sugar usually is less than half the value of the blood sugar in typical cases of bacterial meningitis. The cerebrospinal fluid protein is commonly elevated above 40 mg. per 100 ml. Rarely the cerebral spinal fluid findings are normal or only minimally deranged,<sup>38</sup> especially in the early stages of the disease. A positive culture or smear for bacteria is obviously very helpful in making the diagnosis. However, one must remember that there is approximately a 10 per cent false interpretation of etiologic agent based on cerebrospinal fluid smears.<sup>25</sup>

One of the major problems in diagnosis is that of differentiating aseptic meningitis from partially treated bacterial meningitis. It has long been taught that partial treatment with antimicrobial drugs may change cerebrospinal fluid findings. There may be a shift in the differential count of white blood cells toward an increased number of mononuclear cells, the content of the cerebrospinal fluid sugar and protein may be modified, and cerebrospinal fluid cultures may be less likely to be positive for bacteria. However, this concept has been questioned. Three recent studies<sup>10, 28, 52</sup> indicate that prior therapy does not usually alter mean cerebrospinal fluid values of cells, protein and glucose, but may reduce the number of positive cerebrospinal fluid cultures. *Hemophilus influenzae* is less likely to be inhibited by a brief course of antimicrobial therapy than the other common pathogens.

At least one study<sup>19</sup> indicated that the nitroblue tetrazolium (NBT) dye test is useful in the differentiation of bacterial meningitis from viral and tuberculous meningitis. However, this test was found to be of limited value in partially treated bacterial meningitis and undependable in patients with sickle cell anemia and pneumococcal meningitis. Cerebrospinal fluid creatine phosphokinase activity does not reliably differentiate bacterial meningitis from nonbacterial central nervous system infections.<sup>32</sup>

Determinations of lactic dehydrogenase in the cerebrospinal fluid has also been reputed to aid in differentiating bacterial from aseptic meningitis. One study<sup>10</sup> reported a mean of 14 units in 60 control children, 251 units in 32 children with bacterial meningitis and 23 units in 20 children with aseptic meningitis. The differences between the latter two groups is significant at a *p* value of less than 0.005. In one study, lactic dehydrogenase isoenzymes 1 and 2 appeared to be elevated in viral meningitis while lactic dehydrogenase isoenzymes 4 and 5 were elevated in bacterial meningitis.<sup>7</sup>

When the initial cerebrospinal fluid evaluation leaves some doubt as to the accuracy of the diagnosis of aseptic meningitis, it is helpful to re-

examine the cerebrospinal fluid after a 6 to 12 hour period. After this interval, the cerebrospinal fluid findings in aseptic meningitis will frequently show a shift toward mononuclear cells, whereas in bacterial meningitis the preponderance of polymorphonuclears will persist, and the concentrations of cerebrospinal fluid glucose and protein may change sufficiently to leave little doubt about the correct diagnosis.<sup>1\*</sup> Obviously, if the patient's clinical condition deteriorates before the 6 to 12 hour period has elapsed, repeat examination of the cerebrospinal fluid should be undertaken without delay.

Although the cerebrospinal fluid examination and cultures are crucial, blood cultures are often very helpful in making a definitive etiologic diagnosis.<sup>31, 40</sup> In the experience of Swartz and Dodge,<sup>40</sup> blood cultures were positive in 56 per cent of patients with pneumococcal meningitis, 79 per cent of patients with *H. influenzae* meningitis and 33 per cent of patients with meningococcal meningitis. Examination of smears of material obtained from petechial or purpuric lesions for bacterial organisms may be helpful in establishing the early diagnosis of meningococcal disease. Culture of meningococci from petechial lesions is possible but not frequent.

There have been a number of attempts to increase the rapidity of diagnosis of bacterial meningitis. The use of the smear of the spinal fluid sediment has already been mentioned. Specific fluorescent antibody staining has been used to identify the particular bacterial antigens present in the cerebrospinal fluid.<sup>20</sup> In most studies the results have not been clearly superior to the use of the gram-stained smear. Recently the use of counterimmunoelectrophoresis for identification of cerebrospinal fluid pathogens has been reported with the results being available in approximately 30 minutes.<sup>11, 16</sup> The cerebrospinal fluid is tested against very high titer specific antibody to suspect organisms and the presence of soluble antigen is indicated by a line of precipitate with the appropriate antiserum. Whether this technique will become a useful and practical method for rapid diagnosis of bacterial meningitis remains to be determined. The effectiveness of initial therapy with ampicillin or penicillin, depending on the age group, in large measure may render attempts at rapid diagnosis more academic than practical.

## MANAGEMENT

Management of bacterial meningitis involves a number of considerations other than selection of the proper antimicrobial drug. Some of these include administration of intravenous fluids and electrolytes, and treatment of shock, convulsions or cerebral edema. Requirements for intravenous fluids vary from patient to patient. When hypovolemic shock is present, blood volume expansion with saline, whole blood or 5 per cent albumin may be employed. In the past, pooled plasma was a very useful tool but has been abandoned because of the high risk of transmission of hepatitis. When shock is caused by a cardiac defect, fluid intake should be restricted and use of cardiac inotropic agents may be indicated. When a patient is in shock, placement of a central venous pressure line is an

absolute necessity for monitoring the circulatory status. For intravenous fluids in the patient not in shock, maintenance intravenous fluids suffice until oral alimentation becomes feasible.

The keys to successful antimicrobial therapy are prompt administration, proper route, and adequate dosage with minimal toxicity (Table 1). Initial antimicrobial treatment of bacterial meningitis should be by the intravenous route in all instances, and therapy should be continued for a minimum of 10 days. The drugs of choice for *H. influenzae* are chloramphenicol and ampicillin. The latter is an excellent therapeutic agent against this organism despite the scattered reports of drug failure with this antibiotic.<sup>6, 26, 51</sup> Tetracycline is an alternate drug for therapy of *H. influenzae* meningitis.<sup>11</sup> The antibiotic of choice for meningococcal meningitis is penicillin G, with chloramphenicol an effective alternative drug for patients who cannot tolerate penicillin. The drug of choice for pneumococcal meningitis is penicillin G; chloramphenicol and erythromycin are suitable alternative agents in patients with known hypersensitivity to

**Table 1.** Dosage and Route of Administration of Drugs Employed for Treatment of Hemophilus, Pneumococcal, and Meningococcal Meningitis

ANTIMICROBIAL DRUG	INTRAVENOUS DOSAGE	
	Pediatric	Adult
Ampicillin	400 mg./kg./day in equally divided doses at 4 hr. intervals	12 gm./day in equally divided doses at 4 hr. intervals
Chloramphenicol	100 mg./kg./day in equally divided doses at 6 hr. intervals*	4-6 gm./day in equally divided doses at 6 hr. intervals
Penicillin G	500,000 units/kg./day in equally divided doses at 2-3 hr. intervals	24 million units/day in equally divided doses at 2-3 hr. intervals
Erythromycin#	50-100 mg./kg./day in equally divided doses at 6 hr. intervals	4-6 gm./day in equally divided doses at 4-6 hr. intervals
Tetracycline hydrochloride§	50 mg./kg./day in equally divided doses at 6 hr. intervals	2 gm./day in equally divided doses at 6-8 hr. intervals

\*Drug of choice before organism is identified or when no pathogen is isolated in an obvious case of bacterial meningitis. Drug of choice for listeria meningitis.

\*In premature infants or neonates, the total daily dose should not exceed 25 mg./kg. of body weight.

#The high incidence of phlebitis at sites of intravenous administration may preclude completion of a full course of therapy.

§Other tetracycline analogues are not recommended because of insufficient experience. Five per cent of pneumococci may be resistant to tetracycline. Daily intravenous doses in excess of 2 g. may cause fatal hepatotoxicity. Must be given in reduced dosage in the presence of impaired renal function.

penicillins. The cephalosporins should be avoided as substitutes for penicillin in the treatment of purulent meningitis except possibly in the treatment of pneumococcal meningitis.<sup>35, 50</sup>

The drug regimens employed for initial treatment of the unknown organism have evolved over a number of years. Initially, triple therapy was used—penicillin for the pneumococcus, a sulfonamide for the meningococcus, and chloramphenicol for the *Hemophilus* organism. When sulfonamide resistance became a significant problem with the meningococcus, triple therapy was changed to double therapy consisting of penicillin and chloramphenicol. The development of ampicillin has resulted in its use alone in many institutions for initial therapy of non-hospital acquired bacterial meningitis before the pathogen has been definitely identified. This is quite appropriate in children, but in the individual over 10 years of age where *Hemophilus* is very rare as a causative organism of bacterial meningitis, penicillin G alone is probably adequate initial therapy.

Prophylactic administration of antibiotics to contacts of patients with either *H. influenzae* or pneumococcal meningitis is not indicated. The change in the sulfonamide sensitivity pattern of the meningococcus has removed an effective tool for eliminating carriers or protecting contacts of cases. Penicillin and chloramphenicol, which are very effective in treating meningococcal infections, do not eliminate the carrier state.<sup>41</sup> Close contacts of patients have a greater probability of developing meningococcal disease than the population as a whole; but the actual increase in risk is unknown, and the use of prophylactic chemotherapy remains controversial. Many recommend no prophylaxis unless the organism is sensitive to sulfonamide. Others prescribe sulfonamide prophylaxis regardless of the probability that over 50 per cent of the causative organisms will be sulfa-resistant. Some authorities recommend large parenteral doses of penicillin, arguing that suppression of the meningococci may interfere with disease production even though the bacteria are not eliminated from the nasopharynx. Rifampin and minocycline have been demonstrated to be highly effective in eradicating meningococci from carriers, being active against sulfadiazine-resistant and susceptible strains.<sup>12, 15, 23, 24</sup> Interestingly, rifampin-resistant strains are easily selected from meningococcal cells in vitro, and have been isolated from rifampin-treated carriers.<sup>24</sup> Regardless of whether or not a prophylactic antimicrobial is administered, surveillance of all close contacts of patients with meningococcal disease for early symptoms is mandatory.

Phenobarbital and diphenylhydantoin are the agents usually employed to control seizures in patients with bacterial meningitis. Since there is a delay in the onset of action of diphenylhydantoin, these two drugs are often started together with phenobarbital being discontinued after 1 to 2 days because of the tendency of the latter to induce more sensory clouding than diphenylhydantoin. Diazepam is currently used by an increasing number of physicians and is particularly efficacious in controlling acute convulsions.

The question of the use of steroids is usually raised and is always controversial. The rationale for their use is for the treatment of shock caused by adrenal insufficiency and for prevention of obstructive hydrocephalus

secondary to inflammation and fibrin deposition at the base of the brain. Studies seem to indicate that in the uncomplicated case of bacterial meningitis, steroid levels in the blood are at least normal if not somewhat increased.<sup>37</sup> Whether this increase is enough to meet the stress of bacterial meningitis is not known. Although there may be some indication for the use of steroids in tuberculous meningitis, studies indicate that the use of steroids in the treatment of acute bacterial meningitis does not alter the course or prognosis.<sup>8, 13, 33</sup> One report, however, does raise the question of whether steroids in the acute treatment of pneumococcal meningitis may not improve the ultimate prognosis.<sup>29</sup>

Acute cerebral edema, which is heralded by abnormal pupillary reflexes, respiratory irregularity, opisthotonus or decerebrate rigidity, has been treated by cerebral dehydration or attempts to restore the integrity of the blood-brain barrier using large doses of glucocorticoids.<sup>39, 51</sup> Mannitol is currently the dehydrating agent of choice, having less rebound edema effect than urea. The use of large doses of steroid preparations, such as solucortef or dexamethasone, has not been shown to be of definite value in reducing the brain swelling which may develop during bacterial meningitis. Clearly, the cerebral edema secondary to infection is not as responsive to drug therapy as that associated with acute brain trauma.

Disseminated intravascular coagulation may develop in patients with bacterial meningitis, particularly those with a fulminating meningococcal infection.<sup>14, 36</sup> This phenomenon, which may be associated with a poor prognosis, is suspected clinically when there is the onset of a bleeding diathesis associated with thrombocytopenia, a prolonged prothrombin time, and the depletion of clotting factors V, VII, VIII, and IX. Heparin therapy has been used in attempts to correct the clotting defect,<sup>1, 14, 17, 36</sup> but at present its value in improving the survival rate in fulminant meningococcemia is doubtful.<sup>36</sup>

## COMPLICATIONS

Complications of bacterial meningitis may take many forms which are usually accompanied by persistent or recurrent fever.<sup>25, 49, 51</sup> The more common ones include brain abscess, lateral sinus thrombosis, phlebitis (usually at the site of an intravenous catheter), urinary tract infection, subdural effusion and drug fever. Subdural effusions occur in 10 to 20 per cent of children with bacterial meningitis and are most frequent with *H. influenzae* or *D. pneumoniae*. The patient generally has a recurrence of fever and vomiting after 5 to 7 days of illness; the diagnosis can be corroborated by transillumination, measurement of head circumference and subdural taps along the coronal suture. If fluid is found, it is withdrawn by repeated taps. A neurosurgical consult is indicated if the effusions persist after 2 weeks. Rarely, surgical removal of membranes is necessary, but this approach remains controversial.

Drug fever is not an uncommon finding in a patient who has been doing well for 7 to 10 days and then develops a fever which may be persistent or spiking in nature.<sup>1</sup> The patient usually continues to feel well, has

no other symptoms and repeat lumbar puncture shows a continued change toward normal values. It should be emphasized that this is a diagnosis of exclusion and one must be careful to rule out all other causes of fever. If additional antibiotic therapy is still indicated, treatment can often be continued despite the fever until the antibiotic course has been completed. Withdrawal of the antibiotic almost invariably results in disappearance of the fever. If the reaction is more severe, an alternate drug may be substituted.

## PROGNOSIS

Discussion of the prognosis in bacterial meningitis is hindered by the lack of meticulous follow-up studies which define the precise incidence of neurologic sequelae. Some of the factors predisposing to a poor prognosis include extremes of age, delay in initiation or inadequate duration of therapy, underlying illness such as diabetes, agammaglobulinemia, or sickle cell disease; and seizures, coma, or bacteremia during the course of the illness. Also, the etiologic agent has an effect on the outcome with the pneumococcus probably being the organism with the poorest prognosis. The overall mortality rate is 10 to 20 per cent; that associated with the meningococcus is approximately 6 to 7 per cent, with the pneumococcus 15 to 20 per cent, and with *H. influenzae* 7 to 9 per cent. Sequelae in patients exclusive of the neonate include deafness, hydrocephalus, mental defects, ataxia, epilepsy, and cranial nerve paresis. The overall rate of sequelae is estimated to be 15 to 20 per cent but in most studies these are very gross estimates. Follow-up examinations evaluating such things as learning and behavioral disorders have not been adequately performed.

As far as sequelae with specific organisms are concerned, it is estimated that meningococcus carries a 4 per cent rate, pneumococcus about 25 per cent, and *H. influenzae* about 22 per cent. In the latter regard, retrospective studies<sup>45, 46, 48</sup> tend to indicate that less than half of the victims of *H. influenzae* meningitis escape sequelae. These depressing findings await corroboration by more detailed prospective studies.

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## **Viral Infections of the Central Nervous System**

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Acute viral infections of the central nervous system may present in one of three clinical forms or syndromes: "aseptic" or viral meningitis, poliomyelitis, and encephalitis. Almost all patients with clinically apparent viral infections of the central nervous system can be placed into one or another of these three categories.

In this presentation we will deal primarily with selected aspects of those acute viral infections of the central nervous system commonly encountered in the continental United States. Omitted from this presentation are the arthropod-transmitted viral encephalitides which do not occur in North America, the chronic degenerative diseases associated with so-called "slow" viruses, the post-infectious or allergic encephalitides and rabies. Interested readers will find these topics discussed in several recent reviews.<sup>10, 12, 18, 20, 22</sup>

There are several ways in which etiologic studies may contribute to proper management of acute viral central nervous system infections. First, such studies are essential in selecting patients to be treated with specific antiviral therapy (e.g., idoxuridine in herpes encephalitis); the development of new antiviral agents will make it increasingly important to establish the specific cause in all central nervous system viral infections. Second, only by establishing the etiology in all cases will the entire spectrum of illness associated with each virus be discovered. Third, successfully completed etiologic investigations may be important to the individual patient, especially in those conditions with a predictable clinical course. Finally, adequate documentation may be useful for development of improved public health programs.

### **VIRAL MENINGITIS**

Physicians commonly equate the syndrome of "aseptic" meningitis with that of viral meningitis. Indeed, this practice is even followed by the

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Table 1. *Viruses Responsible for the Aseptic Meningitis Syndrome*

Enteroviruses—	
Polioviruses Types 1, 2, 3	Herpes simplex
Coxsackie A Types 1, 2, 4-11, 14, 16-18, 22-24	Varicella-zoster
Coxsackie B Types 1-6	Lymphocytic choriomeningitis
Echoviruses Types 1-9, 11-25, 30, 31	Encephalomyocarditis
Mumps	Infectious mononucleosis
Arboviruses	

Center for Disease Control of the United States Public Health Service, which publishes periodic reports of *Neurotropic Viral Diseases Surveillance* subtitled "Aseptic Meningitis".<sup>7</sup> However, equating these terms seems ill-advised because bacterial infections (e.g., parameningeal infections, tuberculosis, leptospirosis) requiring specific therapy produce illnesses that may mimic this syndrome. Only when these non-viral conditions have been excluded may "viral meningitis" and "aseptic meningitis" be equated. In his original description of "aseptic meningitis" in 1925, Wallgren recognized the need to exclude bacterial infection in each case.<sup>23</sup> In addition, Wallgren's characterization of the syndrome included acute onset, clinical and laboratory evidence of meningeal irritation, a bacteriologically sterile spinal fluid, and a benign, relatively short uncomplicated course. The clinical picture of most cases of confirmed viral meningitis conforms to this description.

During the years 1963 to 1971, the number of reported cases of "aseptic," presumably viral, meningitis in the United States ranged from 1844 in 1963 to 6480 in 1970. There were 5176 cases in 1971, the last year for which there are complete data.<sup>8</sup> Because of its generally benign character, it is probable that viral meningitis is grossly under-reported and that many of the milder cases are never diagnosed. Under-reporting is less likely with the viral paralytic and encephalitic syndromes because of their more serious and dramatic clinical behavior.

The viruses responsible for aseptic meningitis are listed in Table 1. Over 10 years ago, virologists demonstrated that it is possible to identify the etiologic agent in nearly 75 per cent of cases of "aseptic" meningitis and encephalitis if proper materials are submitted for investigation.<sup>19</sup> In spite of this, in the majority of reports of cases of viral meningitis, the causative organism has not been determined. For example, of the 5176 cases of viral meningitis reported in the United States in 1971, no cause was specified in 3334.<sup>8</sup> On the basis of the author's experience, it is probable that in many cases the agent was not reported simply because no attempt was made to identify it. This failure to seek the cause is understandable in view of the benign nature of viral meningitis, the absence of specific therapy, and the many problems in specimen collection and handling, especially obtaining convalescent phase sera, essential for complete case study. However, for the reasons already specified modern management of this syndrome should include complete etiologic investigations. Furthermore, facilities for such investigations are becoming generally available.

Specimens for viral study of an "aseptic" meningitis syndrome include spinal fluid, stool or rectal swabs, and properly spaced paired sera. It is not essential that samples be bacteriologically sterile, but containers for collecting specimens should be clean and free of contaminating viruses. Since certain viruses are acid-labile, acidic solutions, such as normal saline or dextrose in water, should be avoided when collecting specimens for viral study. Commercial bacteriologic nutrient broth (e.g., brain heart infusion, trypticase soy, etc.), tissue culture media (e.g., Eagle's Medium 199), or a buffered (pH 7.0) solution supplemented with 0.5 per cent bovine serum albumin are suitable for collection and transport of specimens. If delivery to the virology laboratory is delayed for 24 to 48 hours, specimens should be refrigerated (4 °C.); if held longer, specimens should be quick-frozen in a dry ice-alcohol mixture and stored at -70° C. or colder. For optimal results, it is imperative to communicate with personnel in the virology laboratory to become familiar with the preferred methods of handling specimens.

It is worthwhile to collect and save an "acute phase" blood sample in all cases of meningitis of questionable etiology. This sample, properly labeled, may be stored for several days in a refrigerator until it is decided if viral studies are in order. With that decision, the sample should be centrifuged and the serum frozen at -20° C. or colder until the convalescent serum is obtained at least 7 to 10 days later. If possible, an interval of several weeks is even more appropriate.

One should be circumspect about prematurely discarding an "acute phase serum" in an appropriate clinical situation. Crawford and his associates<sup>8</sup> have reported that the earlier the acute phase serum is obtained, the higher the incidence of significant antibody titer rises in patients with viral meningitis. When the initial serum specimen was obtained by the fifth day of the illness, significant antibody titer rises were observed in 89 per cent of the patients. When the initial serum specimen was obtained after the fourteenth day, significant rises in antibody titer were found in only 16 per cent of the patients.

One of the more difficult diagnostic problems in clinical virology is the collection of appropriate "convalescent phase" sera. Serodiagnosis, which is a major tool for establishing the identity of etiologic agents in all the viral syndromes, is almost totally dependent on the availability of such "convalescent" sera. Even where serodiagnosis is less useful, as in enteroviral infections, it is essential for evaluating the significance of enteroviral isolates from stool or similar specimens.

Some of the obstacles in collecting "convalescent sera" are fairly obvious. Generally, 4 to 6 weeks after onset, when these samples should be obtained, the patient is well and both he and his physician are no longer as concerned about the cause of the illness from which he's recovered. The fact that many of these patients are young children further influences the blood-drawing procedure. Only if the physician acknowledges the validity and importance of pursuing the specific cause will he make an appropriate effort to obtain the needed serum.

Various enteroviruses and mumps are the etiologic agents most frequently identified in "aseptic" meningitis when viral studies are properly conducted. In 1971, of the 5176 cases reported to the Center for

Disease Control, an etiologic agent was identified in 739.<sup>5</sup> An enterovirus was associated with 611 or 82 per cent of these cases and mumps with an additional 90. Thus, in 95 per cent of the small number of cases with which a virus was associated, the agent was either an enterovirus or mumps. However, enteroviruses and mumps did not predominate in the more intensive etiologic investigations mentioned earlier.<sup>17, 19</sup>

In these studies, a causal virus was identified in up to 75 per cent of the patients, but mumps and enteroviruses accounted for only 50 per cent of the total cases. Both mumps and the enteroviruses display marked seasonal variations in frequency, mumps being most prevalent in winter and spring and the enteroviruses in summer and fall. This seasonal variation in the incidence of the two most common causes of the meningitis syndrome may permit an "educated guess" regarding the cause of a given case, but both occur throughout the year and it is not possible clinically to distinguish cases of the mumps syndrome from those due to enteroviruses in the absence of parotitis.<sup>5, 17</sup> Age is of little value in discriminating among the causes of the viral meningitis syndrome, although in most of the reported cases, regardless of etiology, patients are less than 20 and a large majority less than 40 years of age.<sup>5</sup>

Figure 1 illustrates that cases of "aseptic" meningitis of unknown etiology have a seasonal distribution similar to that of the cases of confirmed enteroviral or other known cause. Had they been completely studied, it is likely that one or another of the commonly found agents would have been identified.

It can not be overemphasized that the clinician faced with a case of "aseptic" meningitis is obligated to rule out septic and other treatable causes of the syndrome. This may be difficult if the patient has had prior antibiotic therapy. Cerebrospinal fluid profiles have overlapping features in many instances.<sup>25</sup> Early in the course of viral meningitis, polymorphonuclear leukocytes may predominate in the spinal fluid. Cases of bacterial meningitis with modest elevations in cerebrospinal fluid protein and with normal or only mildly depressed cerebrospinal fluid sugar are not rare. If one cannot confidently rule out partially treated bacterial meningitis, it is necessary to treat with antibiotics.

Although a benign and uncomplicated course was part of Wallgren's original description of "aseptic" meningitis, complications and even mortality may be associated with this syndrome. In 1971, there were 30 deaths among the 4073 cases which were completely reported to the Center for Disease Control. Lepow et al.<sup>17</sup> found evidence of some degree of disability in about half of 301 patients who were adequately evaluated following hospitalization with "aseptic" meningitis. Many patients required weeks to months for complete recovery from the acute illness although by one year less than 5 per cent had any residual disability. The most frequent objective residuals were muscle tightness and weakness demonstrated on formal muscle testing. Lepow and her colleagues<sup>17</sup> recommended that patients have a thorough muscle evaluation about 2 months after discharge and that patients and their families be advised that the ultimate prognosis for complete recovery is excellent.

Proper management of viral meningitis does not require routine follow-up lumbar punctures. It is the author's experience that cerebro-

spinal fluid pleocytosis and protein concentrations fluctuate considerably during recovery. Because of this, follow-up lumbar punctures often generate more anxiety than they shed light on the patient's condition. Barring other clinical indications, only the initial lumbar puncture is needed to establish the diagnosis and to provide spinal fluid for etiologic studies.

The indications for hospitalization of patients with the viral meningitis syndrome merit some comment. Because treatment is primarily supportive and symptomatic, in cases where there is little or no uncertainty about the diagnosis and the patient is not very ill, hospitalization is not mandatory. However, it is not acceptable to manage patients with definite signs of meningeal irritation without examining the spinal fluid and observing the patient fairly closely. These latter objectives are the usual immediate goals of hospitalization.

Hospitalizing these patients raises questions about isolation which are not always easy to answer. Enteroviruses, which are the most common cause of viral meningitis do not seem to spread readily to other patients or personnel within the hospital.<sup>17</sup> Handwashing and adequate personal hygiene seem to be sufficient to prevent transmission. However, because initially the specific etiology is usually in doubt, isolation is recommended at least until it becomes clear that the patient does not require it.

### POLIOMYELITIS SYNDROME

Poliomyelitis has essentially disappeared from the United States since the widespread administration of the poliovirus vaccines. There were just 29 cases reported in the United States in 1972.<sup>1</sup> However, the question of whether and for how long this favorable situation will continue has been raised by a provocative paper by Gold et al.<sup>9</sup> These authors detected very low poliovirus antibody titers in 57 per cent of a population of young children, despite the fact that about half of this low titer group had been immunized in accordance with recommended procedures.

Poliomyelitis presents as viral meningitis plus paralysis. Paralysis is really the only distinguishing feature. In the days of epidemic poliomyelitis, the "aseptic" meningitis syndrome was often referred to as "non-paralytic polio." Unlike the "aseptic" meningitis syndrome, however, poliomyelitis is etiologically associated only with mumps and a small number of other enteroviruses (Table 2), the polioviruses accounting for essentially all the cases. The nonpolioviruses listed in Table 2 are very infrequent causes of paralytic disease in this country; in some instances their inclusion on the list is based on a single case in which virus was not recovered from the cerebrospinal fluid, leaving the association in doubt.<sup>11</sup>

**Table 2.** *Viruses Causing the Poliomyelitis Syndrome*

Polioviruses Types 1, 2, 3	Echoviruses Types 1, 4, 6, 9, 11, 16, 30
Coxsackieviruses A Types 4, 7, 9, 10	Mumps
Coxsackieviruses B Types 1, 5	

The diagnostic procedures discussed above for "aseptic" meningitis syndrome are recommended for poliomyelitis as well. It is now more important than ever to investigate paralytic cases because the cause is no longer as predictable and because of concern about the potential resurgence of poliomyelitis. A small number of cases seen each year appear to be related to the administration of live poliovirus vaccine, and it is very important to investigate thoroughly each of these cases to confirm or rule out an etiologic association with the vaccine virus.

Poliomyelitis presents special problems in relation to the management of paralyzed muscles, particularly when muscles controlling breathing and swallowing are involved. When poliomyelitis was epidemic, special centers were established for the care of such patients. The problems created by these paralyzed patients, both physical and psychological, are extremely complex, and considering the current rarity of the poliomyelitis syndrome, the interested reader is referred to detailed discussions by Weinstein<sup>24</sup> and Howe and Wilson.<sup>13</sup>

Although there is no specific therapy, all patients with the poliomyelitis syndrome should be hospitalized to establish the diagnosis and to ensure optimal management of the paralyzed muscles. Bulbar paralysis is an absolute indication for hospitalization, ideally in a center experienced in handling such patients. Isolation procedures, previously discussed for patients with enterovirus infections, are no different for the poliomyelitis patient.

The availability of effective and safe prophylactic agents has shifted the emphasis in management of this syndrome from treatment to prevention. Each physician has a responsibility to see that all patients under his care are adequately immunized. The currently recommended immunization procedures are described in detail in a recent Center for Disease Control publication.<sup>3</sup> A widely used and approved immunization program consists of 3 doses of trivalent, live, oral poliovirus vaccine, the second dose given 6 to 8 weeks after the first, and the third 8 to 12 months later. Poliovirus immunization programs have been dramatically successful in this country and in many parts of the world and hopefully the observations of Gold et al.<sup>9</sup> do not indicate that this situation is about to change.

## ENCEPHALITIS

The third viral syndrome affecting the central nervous system is encephalitis, distinguished from viral meningitis by the presence of obvious cerebral dysfunction, including altered states of consciousness, abnormal behavior and mental function with prominent memory defects and/or seizures, in addition to the fever, headache, and cerebrospinal fluid abnormalities characteristic of all viral central nervous system infections. The term "meningoencephalitis" implies the presence of both meningeal and encephalitic features; though widely employed, it adds little to our understanding of the disease process, since the manifestations of encephalitis usually predominate.

Viral encephalitides may present in either an acute or a subacute fashion; fluctuations in cerebral abnormalities occur rapidly and are

often pronounced. Coma and convulsions pose serious problems for the clinician. In this country, differential diagnosis includes brain abscess and central nervous system infection caused by fungi and *M. tuberculosis*. It is particularly important to rule out these other infections and attempt to establish a specific viral diagnosis in every patient with an encephalitis syndrome, since potentially beneficial specific therapy is available for infections due to herpes simplex virus.<sup>15</sup> There are no etiologically specific clinical features which discriminate among the many viruses that cause encephalitis (Table 3), although certain features may be characteristic of groups of cases caused by different agents. However, in the management of single cases occurring apart from a recognized epidemic, clinical data alone are inadequate to establish an etiologic diagnosis with sufficient certainty to justify the use of highly toxic substances such as idoxuridine.

All patients with suspected encephalitis should be hospitalized and isolated in the manner previously discussed. Diagnostic investigations should include brain scan, at least in those more seriously ill. Cerebral arteriograms and pneumoencephalograms may be indicated when focal signs are prominent. "Acute" and "convalescent" phase serum samples should be obtained in every case of suspected encephalitis as in the other acute viral central nervous system syndromes. Spinal fluid and other appropriate specimens should be submitted for virologic study as discussed above.

The remainder of this discussion will be confined to herpes simplex virus encephalitis because this infection has stimulated more widespread interest in the medical community than any of the other specific viral encephalitides. Much of this interest is due to the possibility that idoxuridine is an effective form of therapy for this frequently fatal or crippling disease. For a more detailed consideration of the other encephalitides listed in Table 3, the reader is referred to two recent reviews.<sup>10, 20</sup>

Herpes simplex virus is probably one of the most frequent causes of sporadic cases of serious encephalitis in the adult.<sup>21</sup> Serious encephalitis implies coma, convulsions, or both. Although the incidence curve of viral

**Table 3.** *Viruses Causing Acute Encephalitis Syndrome*

Arboviruses	
Eastern equine	Russian spring-summer
Western equine	Japanese B
St. Louis	Powassan
Venezuelan equine	West Nile
California	Murray Valley
	Louping ill
Enteroviruses—Echo, Coxsackie, Polio	
Others	
Mumps	Rabies
Herpes simplex virus	Cytomegalovirus
Herpes B virus	Rubella
Varicella-zoster	Infectious mononucleosis
Rubeola	

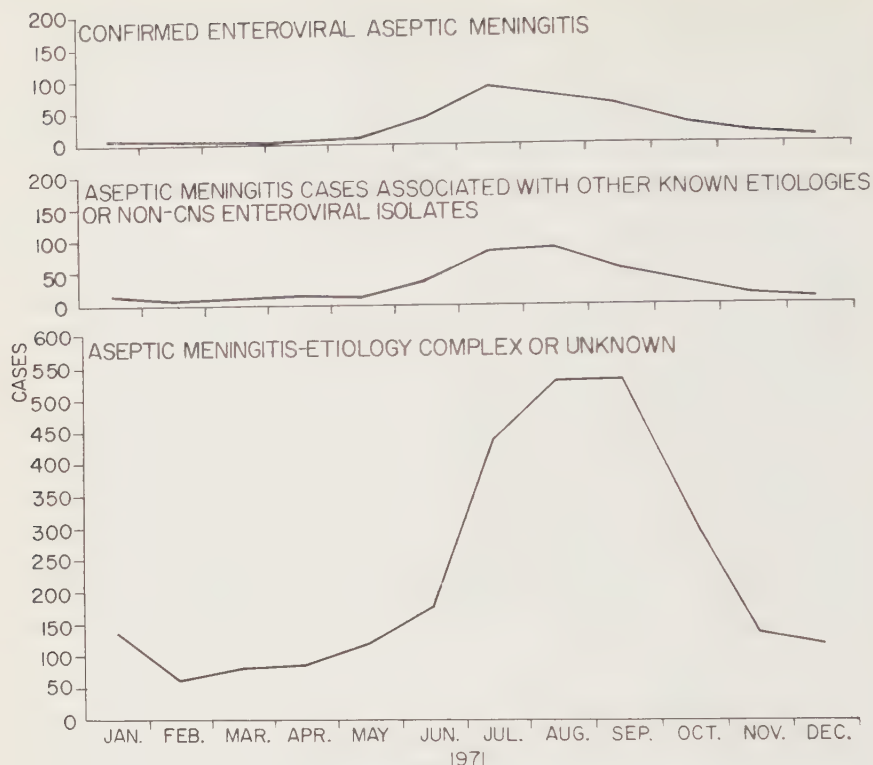


Figure 1. Cases of Aseptic Meningitis\* in 44 Reporting Areas, by Month of Onset and Etiologic Group, 1971. (From Neurotropic Viral Diseases Surveillance. Aseptic Meningitis. Annual Summary 1971. Center for Disease Control, U.S. Department of Health, Education and Welfare, May 1973, by permission.)

encephalitis is similar to that for "aseptic" meningitis with a peak in summer and fall (Fig. 1), herpes encephalitis occurs at a constant rate throughout the year and serious encephalitis in winter and spring is somewhat more likely to be herpetic. In the summer and fall, enteroviruses and arboviruses probably account for the seasonal increase. However, only a small fraction of the reported cases of encephalitis in this country are ever etiologically diagnosed.<sup>10</sup> It has been estimated that herpes simplex virus causes 10 per cent of the total number of encephalitis cases.<sup>21</sup>

Some investigators have commented on the presence of recurrent herpes labialis in herpes encephalitis.<sup>16</sup> Although encephalitis undoubtedly occurs in patients with recurrent herpes simplex infections, this must be relatively uncommon and, therefore, this sign is of little clinical value.<sup>10</sup>

Patients with herpes simplex encephalitis frequently present with signs of temporal lobe involvement and evidence suggesting a temporal mass. Indeed, encephalitis with manifestations of a temporal mass

suggests the possibility of herpes simplex encephalitis. The cerebrospinal fluid findings are quite variable, may even be normal, and do not distinguish herpes simplex virus from other causes of encephalitis. In the final analysis, the specific etiologic diagnosis can be established only by virologic methods.

Establishing a virologic diagnosis is complicated by the fact that the virus is rarely recovered from the cerebrospinal fluid of adults with herpes encephalitis. Absence of the virus from the cerebrospinal fluid in encephalitis beyond the age of infancy seems to be due to the mode of central nervous system invasion by the nongenital or type 1 herpes simplex virus which causes such encephalitis. In contrast, the virus is frequently recovered from the cerebrospinal fluid of newborn infants with the disseminated herpes simplex virus syndrome, an infection caused by the genital or type 2 virus. In adults, "aseptic" meningitis generally results when type 2 herpes simplex virus invades the central nervous system, whereas the type 1 virus produces encephalitis. Type 1 and type 2 viruses probably invade the central nervous system by different mechanisms, the type 2 viruses being blood-borne.<sup>7</sup>

Diagnosis is also hampered by the absence of specific serologic tests capable of detecting early cases. Therefore, the only way to establish the diagnosis unequivocally is by demonstration of herpes simplex virus in brain biopsy specimens. The indications for brain biopsy in suspected herpes encephalitis were recently summarized.<sup>10</sup> Briefly stated, herpes encephalitis must be the best working diagnosis based on cerebrospinal fluid findings and on a clinical illness with subacute onset, fever, signs of cerebral dysfunction, and focal neurologic deficits. The indications for biopsy are enhanced when there is evidence of a mass lesion, particularly in the temporal lobe.

Although the diagnosis of encephalitis due to herpes simplex virus may be strongly suspected on the basis of routine histologic studies, the biopsy should be studied with fluorescent antibody stains and processed to recover virus in cell cultures and/or eggs. Fluorescent antibody stains yield information in a few hours and virus is isolated from cell cultures as early as 1 to 3 days. However, biopsy should not be undertaken unless arrangements have been made for prompt virologic study of the tissue, before therapy is started with idoxuridine or cytosine arabinoside. The specimen, preferably from the temporal lobe, should be placed in no fixative or transporting solution but processed as soon as possible. If a delay is unavoidable the specimen should be quick-frozen and stored at  $-70^{\circ}\text{C}$ . or colder. Moreover, the author believes that chemotherapy for suspected herpes simplex encephalitis should not be administered without first obtaining a brain biopsy for culture in order to establish the diagnosis because additional study of drug efficacy in confirmed cases is needed.<sup>15</sup>

Treatment of herpes simplex encephalitis with idoxuridine was first reported in 1966 and was based on laboratory studies and benefits from its topical use in the treatment of herpetic keratitis.<sup>2</sup> Idoxuridine is a thymidine analogue which interferes with DNA synthesis essential for the replication of herpes simplex virus, a DNA virus. Likewise the toxicity of the agent seems to be based on its ability to interfere with host-cell DNA synthesis. The drug is available only for investigational use and

is supplied by Calbiochem of Los Angeles, California. The drug is usually given intravenously in a dose of 100 mg. per kg. per day for 5 days. Some investigators recommend that the infusion be administered continuously for the entire 24 hour period, but other schedules have been used.

The bone marrow (leukopenia and thrombocytopenia), the skin and its appendages (alopecia), and the gastrointestinal tract mucosa (diarrhea) are the usual sites of drug toxicity, which fortunately is readily reversible and usually mild. Hepatotoxicity may also occur. Toxicity may not develop until after the drug has been stopped. The functional status of these organs should be monitored frequently during and following therapy until all have returned to normal. Nolen and his associates<sup>21</sup> found no serious toxicity when the total dose did not exceed 20 gm. of idoxuridine (54 mg. per kg. for 5 days), given in 45 to 60 minute infusions every 12 hours. Cytosine arabinoside has also been used experimentally to treat herpes simplex encephalitis.<sup>6</sup>

The variable course of herpes encephalitis is a major obstacle to clear-cut evidence of therapeutic efficacy for idoxuridine and cytosine arabinoside.<sup>15</sup> Although herpes simplex encephalitis produces considerable mortality and residual neurologic disability in survivors, mild cases occur and comatose patients occasionally recover without antiviral chemotherapy.<sup>11, 20</sup> Hopefully, current large-scale cooperative studies will soon provide answers to this question.

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## Infective Endocarditis

### A Review of Selected Topics

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The changing nature of infective endocarditis has been the subject of many reviews in the past 10 to 15 years.<sup>18, 55, 62, 100, 108</sup> Interest in the disease remains high, for in spite of effective antimicrobial chemotherapy, its patterns continue to evolve. Recent surgical advances provide a means for saving patients whose damaged hearts might otherwise fail or in whom antibiotics have failed. The great promise of surgery must be tempered, however, by reports such as one recent autopsy series in which the diagnosis remained elusive during life in a significant number of instances, and in which infection, rather than congestive heart failure, re-emerged as a major cause of death, particularly in relation to infections associated with cardiac prostheses.<sup>29</sup> While the mean age of patients with infective endocarditis has risen sharply over the past three decades, clusters of cases among younger patients with infective endocarditis consequent to narcotic addiction and cardiac surgery have emerged.<sup>18</sup>

The many clinical variants and modes of presentation continue to foster misdiagnoses. Severe musculoskeletal back pain, an infrequent presenting complaint, is not widely appreciated.<sup>19</sup> Neurologic presentations in particular misdirect the clinician.<sup>110</sup> Unusual etiologic organisms continue to be recorded, often as a result of prior therapies, and have led to the designation "infective endocarditis" replacing subacute bacterial endocarditis or bacterial endocarditis in most reviews. Such benign non-pathogenic organisms as *Lactobacillus* and *Bacillus* species have been responsible for spontaneous cases of subacute bacterial endocarditis.<sup>1</sup>

When considering dental care in patients with valvular heart disease or a past history of subacute bacterial endocarditis, it is worth noting that oral irrigation devices currently in vogue for home use have been demonstrated to induce bacteremias, primarily with streptococci, in 50 per cent of a small group of patients with periodontitis.<sup>41</sup> Even in the presence of a chronic but mild gingivitis, organisms may gain entry to the blood follow-

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ing the use of these devices.<sup>91</sup> Thus, recommendations for dental prophylaxis must now extend beyond the dentist's office.

While it is obvious that many facets of endocarditis provoke interest, the author has chosen to survey only a few selected aspects of this disorder worthy of particular emphasis to a general medical audience.

## CULTURE-NEGATIVE INFECTIVE ENDOCARDITIS

The incidence of negative blood cultures in infective endocarditis varies with the criteria employed by different reviewers.<sup>44-45</sup> Some evidence suggests that the proportion of patients with infective endocarditis and persistently sterile blood cultures is increasing, chiefly because of prior exposure to antibiotics. Patients with negative blood cultures have longer histories of illness and more embolic episodes than those with positive cultures.<sup>45</sup> Blood cultures are usually positive in the acute form of right-sided endocarditis, although they are often negative in right-sided subacute bacterial endocarditis.<sup>62, 88</sup>

Febrile patients with valvular or congenital heart disease pose a difficult problem for the physician. Many patients treated for subacute bacterial endocarditis actually have pneumonia, pulmonary infarction, systemic emboli, active rheumatic fever, the "pump" or postpericardiotomy syndrome, or systemic lupus erythematosus.<sup>41</sup> Otherwise unexplained microscopic hematuria is a valuable clue in a suspect patient and its absence makes the diagnosis questionable.<sup>100</sup>

When blood cultures are negative in suspected cases of infective endocarditis the patient is usually treated with penicillin and streptomycin as though enterococci were present.<sup>55, 58, 62</sup> Whether penicillin-susceptible bacteria other than streptococci might be responsible for some cases that respond favorably to empiric penicillin-streptomycin therapy has not been the subject of any systematic review. Prior exposure to antimicrobials is most frequently blamed for failure to recover pathogens, but other technical and etiologic considerations should be entertained when the physician alerts the bacteriology laboratory to a possible case of infective endocarditis.<sup>62</sup> Valuable serologic tests are frequently overlooked.

"Bacteria-free" subacute bacterial endocarditis was not uncommon in the pre-antibiotic era, when long-term untreated survivors might enter a chronic and possibly immunologically derived phase associated with renal and/or congestive heart failure, in which bacteria could no longer be recovered, even at autopsy. These patients were markedly pigmented, anemic, often afebrile, had large spleens, and usually died of renal failure or emboli. Such cases are seldom if ever seen currently, but subacute bacterial endocarditis should be considered in any patient with renal failure of uncertain etiology, even if fever is minimal or absent.<sup>62</sup>

This is also true in what might be considered a modern counterpart of such cases, patients with renal failure undergoing chronic hemodialysis. Subacute bacterial endocarditis may be more common than previously suspected in this group.<sup>57, 90, 93</sup> Uremia somehow masks fever and fosters negative blood cultures.<sup>62</sup> Acquired arteriovenous fistulas predispose animals and man to spontaneously acquired bacterial endocarditis,<sup>56</sup> so

not surprisingly bacterial endocarditis has been associated with chronic hemodialysis, since the shunt provides the fistula as well as a ready source for subsequent contamination of blood. The shunt probably becomes infected first, although few have been examined histologically in patients on dialysis who have developed bacterial endocarditis. Staphylococci and streptococci are the most frequent offenders.<sup>57, 90, 93</sup> Since hematuria, anemia, and murmurs associated with anemia are commonplace in uremia, these signs will not alert the physician in patients on hemodialysis with unexplained fever but negative blood cultures. The incidence of unsuspected bacterial endocarditis in such patients is uncertain, but the author finds that empiric antibiotic therapy directed against gram-positive pathogens occasionally produces defervescence in patients on hemodialysis who develop chronic unexplained low-grade pyrexia.

Q fever endocarditis, reported from England and Australia since 1959, may produce gross valve distortions, large fungating vegetations, and even ventricular aneurysms.<sup>13</sup> One case may have persisted over a 6 year interval;<sup>116</sup> *Coxiella burnetti* has even infected cardiac prostheses<sup>79</sup> and has been demonstrated in a surgically removed iliac artery embolus.<sup>117</sup> Complement-fixation tests against *C. burnetti* antigens are usually necessary to establish the diagnosis while the patient is still alive; a prozone phenomenon may be present, so adequately diluted serum must be tested.<sup>13</sup> At least one case, a fatal one, has been seen in this country.<sup>89</sup>

Two fatal cases of endocarditis caused by the agent of psittacosis (Bedsonia or *Chlamydia psittaci*), with prominent finger-like vegetations on the valves, also reported from England, suggest that a history of pneumonitis and bird contact should initiate serologic studies for this agent in patients with infective endocarditis but negative cultures.<sup>63</sup>

Evidence for a viral etiology in problem cases of endocarditis is lacking, but several viruses are known to cause valvular damage in experimental animals.<sup>11</sup> Valvulitis produced in mice and monkeys with Coxsackie B viruses histologically resembles that seen in human rheumatic valvular disease; viral antigen was present in damaged valves for up to 200 days post inoculation. Coxsackie B<sub>3</sub> antigen has been demonstrated in a pathologic mitral valve in man.<sup>12</sup> Viral crystals of encephalomyocarditis virus are present in cardiac valves of experimentally infected mice.<sup>10</sup> A routine search for viruses, perhaps utilizing newer techniques, should be undertaken at surgery and autopsy in cases of valvular vegetations of uncertain etiology. Endocardial vegetations seen at autopsy in patients with poliomyelitis strongly favors the concept of viral endocarditis in man.<sup>111</sup> Inclusion cells have recently been described in mural ventricular vegetations in a fatal case of disseminated cytomegalovirus infection following chemical burns in a 13 year old Negro boy; extensive myocarditis was also present.<sup>85</sup>

Cell wall-defective bacterial variants must be considered in suspect patients previously exposed to antibiotics: cultures in osmotically stabilized media are in order. Both active and latent infections have been associated with L-forms in patients with infective endocarditis; staphylococci, *Str. fecalis*, corynebacteria, and candida species have been recovered.<sup>64, 81, 92</sup> Without debating the issue of primary pathogenicity for

these bacterial variants, it is apparent that cultures cannot be truly defined as negative if the suspect patient has recently received antibiotics unless the blood has been incubated in appropriate hypertonic media.<sup>71</sup>

More rigorous anaerobic culture techniques would undoubtedly disclose additional cases of bacterial endocarditis caused by fastidious or slowly growing anaerobes.<sup>35, 80</sup> Since many anaerobes are susceptible to penicillin, these patients might also respond favorably to empiric penicillin-streptomycin therapy. Not a single anaerobic gram-negative organism was implicated among a total of 1239 cases from 6 large series of bacterial endocarditis.<sup>80</sup> Although most of the 37 reported cases followed a subacute course, the anaerobic gram-negative bacilli appeared to be more invasive and destructive than "viridans" streptococci; *Fusobacterium necrophorum* is capable of causing an acute endocarditis.<sup>80</sup> Embolic phenomena were prominent complications (67 per cent); *Bacteroides oralis*, *B. melaninogenicus*, *F. necrophorum*, *F. nucleatum* were among the penicillin-susceptible gram-negative anaerobes reported, but anaerobic streptococci are also usually quite sensitive to penicillin.<sup>35, 80</sup> *Bacteroides* species may grow very slowly, so cultures should not be discarded for at least three weeks.<sup>55, 60</sup> *Eubacterium* species, another penicillin-susceptible organism, have recently been recovered from patients with subacute bacterial endocarditis when appropriate anaerobic cultures were obtained.<sup>95</sup>

In a case of subacute bacterial endocarditis known to the author, accidental contamination of a subculture plate by an optochin disc revealed the presence of satelliting streptococci in blood cultures otherwise considered negative. Satelliting streptococcal bacteremia and endocarditis has recently been reported<sup>7</sup> and thiol-requiring satelliting streptococcal mutants were recovered in 3 cases of subacute bacterial endocarditis in France.<sup>16</sup>

Uncommon agents causing subacute bacterial endocarditis are *Cardiobacterium hominis*, *Hemophilus aphrophilus* and *Actinobacillus actinomycescomitans*, similar slow-growing, tiny, pleomorphic, gram-negative coccoid to coccobacillary organisms, which grow poorly or not at all in the absence of carbon monoxide and may be missed entirely (in the case of *H. aphrophilus* and *Actinobacillus*) if the culture flask is not carefully tipped to reveal the tiny colonies growing at the fluid glass interface, rather than diffusely through the broth.<sup>77, 83</sup> Obviously, the bacteriology laboratory must be alerted to this possibility. Four cases caused by these uncommon pathogens seen in this community in less than 2 years suggest they may not be as rare as scattered reports suggest. Since these patients may respond to penicillin alone or in combination with streptomycin, some cases in which cultures are negative might be due to these organisms.

Carbon dioxide incubators should be standard equipment in all hospital bacteriology laboratories, but they are not. The fortuitous recovery of a carbon dioxide-dependent dwarf colony of staphylococcus, while looking for brucella in a case of bacterial endocarditis, suggests that this simple maneuver should not be overlooked.<sup>104</sup>

The question of culture-negative *Staph. aureus* endocarditis should

be raised. The author has seen a typical case of acute destructive aortic valve endocarditis in a pregnant woman, with an abrupt onset several weeks following an untreated and unattended suppurating knee injury. Blood cultures were consistently negative, but antibiotic therapy (methicillin and kanamycin) effected a clinical cure over a 5 week period prior to replacement of the aortic valve. The destroyed valve was grossly compatible with acute bacterial endocarditis. In similar cases, it might be prudent to look for teichoic acid antibodies, as found in 14 of 15 patients with proven staphylococcal endocarditis and 50 per cent of patients with staphylococcal bacteremia, but no clinical evidence of endocarditis.<sup>23</sup> The latter figure approximates the autopsy incidence of clinically unsuspected bacterial endocarditis in patients dying of staphylococcal sepsis.<sup>111</sup> Others have recorded deaths following a fulminating picture of infective endocarditis despite persistently negative blood cultures.<sup>45</sup>

In high-risk patients who have undergone cardiac surgery, serologic monitoring for precipitin and agglutinating antibodies to cytoplasmic candida antigens has been suggested as a means of early detection for postcardiotomy candida endocarditis, where blood cultures may be persistently negative both early and late in contrast to the ready growth of candida in blood cultures when this mycotic endocarditis is acquired by narcotic addicts or as a superinfection during intravenous antibiotic therapy for subacute bacterial endocarditis.<sup>75, 97</sup>

Valve involvement is generally but one feature of widespread infection in most disseminated mycotic infections and is usually unsuspected during life.<sup>26</sup> Less unusual is the occurrence of endocarditis in histoplasmosis; at least 18 cases have been reported.<sup>98</sup> Meningitis, a rare manifestation of histoplasmosis, has occurred in association with histoplasma endocarditis on at least five occasions.<sup>39</sup> *H. capsulatum* is difficult to isolate from blood, even in dogs with experimental histoplasma endocarditis, so complement-fixation tests for histoplasmosis should be considered in cases of infective endocarditis with negative blood cultures. Urine, lymph node, or bone marrow cultures may also be helpful.<sup>75</sup>

No feature of fungal endocarditis is more characteristic than the marked tendency for embolic occlusion of large arteries, since the vegetations are very large and friable.<sup>97</sup> Embolectomy from an accessible artery is a diagnostic as well as a therapeutic maneuver since frequently this may be the only means of recognizing the diagnosis. Aspergillus, histoplasma, and candida have been recovered in this fashion.<sup>37, 97, 98</sup> Blastomycotic endocarditis is rare and usually results by direct extension from an obvious pulmonary or mediastinal blastomycotic lesion; rarely the pulmonary focus is not recognized while cardiac symptoms predominate.<sup>75</sup> Endocarditis associated with aspergillus species is also characterized by negative blood cultures except for some few cases following cardiac surgery.<sup>37, 55, 76</sup> The range of unusual fungal species that may infect patients with cardiac prostheses includes some unfamiliar, seldom pathogenic fungi, such as *Curvularia geniculata*,<sup>52</sup> *Hormodendrum dermatitidis*,<sup>31</sup> *Paecilomyces varioti*<sup>101</sup> and *Coprinus*, of the toadstool group of fungi.<sup>102</sup> It is important that the laboratory not discard any unusual organism as an exogenous contaminant, if and when they finally grow in routine blood cultures.

## INFECTIVE ENDOCARDITIS OF THE MURAL ENDOCARDIUM

Reports citing infected mural endocardial lesions, without associated valvular vegetations, have been more frequent in recent years, and not unexpectedly, iatrogenic factors often play a role. Aside from mural infection associated with congenital heart lesions, particularly with ventricular septal defects, until quite recently the only other significant example of mural infection was the rare case of spontaneous infection of a mural thrombus overlying a myocardial infarction.<sup>15</sup> The organisms involved were usually other than streptococci, and particularly salmonella species in association with ventricular aneurysms,<sup>72-82</sup> but also staphylococci and candida species. Abscess formation within a myocardial infarction is also a rare event, but such lesions may extend to the endocardial surface. Unusual organisms are also characteristic and include bacteroides, coagulase-negative staphylococci, and *E. coli*.<sup>14, 15</sup> Atrial myxomas may become infected and produce a picture of subacute bacterial endocarditis, either with streptococci or more resistant organisms, such as staphylococci, *Str. fecalis*, or candida, but even uninfected myxomata may produce the same picture.<sup>65, 106</sup>

In patients with leukemia or lymphoma, extension of mycotic infection (candida, mucor, aspergillus) from one or more myocardial abscesses onto the mural surface of either ventricle or into the right atrium via the pulmonary veins from pulmonary abscesses may occur as part of a generalized fungal septicemia.<sup>9</sup> Although not usually a direct cause of death, cardiac rupture, aortico-right ventricular fistulas, or systemic embolization may occur. Surprisingly, blood cultures may be negative even when candida species are involved.<sup>9, 78</sup> The same pathologic sequence may involve the mural endocardium in other debilitated patients as part of a generalized septic process.<sup>15, 78, 85</sup> Unusual pathogens, such as *E. coli*, coagulase-negative staphylococci, group C beta-hemolytic streptococci, and a cytomegalovirus have been involved.

Infected mural right atrial lesions, with or without associated tricuspid valve involvement, may be a complication of permanent or temporary cardiac pacemakers.<sup>96</sup> The incidence of this complication is uncertain, but the author encountered 3 such cases, all unreported, in less than a 2 year span; faulty insertion technique was unquestionably responsible for one case. Central venous pressure catheters also may produce this picture.<sup>9</sup> Staphylococci and candida are the most frequent offenders and removal of the foreign body is usually necessary to achieve a cure.

Such cases may be seen more frequently with widespread use of pacemakers and central venous pressure catheters in a vulnerable cardiac population, particularly when sterile technique and a surgical attitude are ignored during their insertion. Rarely, a foreign body, such as a piece of a catheter<sup>110</sup> or a wire, finds its way to the ventricular endocardium via the systemic circulation and initiates a similar process, again with resistant organisms, such as candida and coliforms.<sup>73</sup>

Two cases of left atrial mural endocarditis, without valvular involvement, were seen in a series of 21 patients with pseudomonas endocarditis resulting from intravenous use of heroin.<sup>86</sup> Large emboli to the femoral arteries occurred in both patients.

In the presence of left ventricular hypertrophy, chronic obstructive pulmonary disease, or Marfan's syndrome, certain patients may develop friction plaques on the left ventricular endocardium from the action of apposing chordae tendinae, either just beneath the septal leaflet of the tricuspid valve or on the wall of the left ventricle beneath the posterior leaflet of the mitral valve. It is noteworthy that in this infection-prone lesion, the first reported case involved staphylococcal infection of such a plaque in a young woman with none of the aforementioned antecedents.<sup>60</sup>

## NARCOTICS-ASSOCIATED INFECTIVE ENDOCARDITIS

Addicts using heroin intravenously rarely observe antiseptic precautions, and frequently share and re-use syringes and needles. Cleansing of the skin is uncommon and the injection of heroin may be prepared with tap water or even saliva.<sup>21</sup> Therefore local skin infection and thrombophlebitis are common and subsequent systemic sepsis and infective endocarditis not uncommon sequelae.

Endocarditis complicating narcotics addiction presents some unique features when compared to infective endocarditis in general, besides involving a younger group of patients. In a review of 60 published cases, 40 per cent of patients had involvement of the tricuspid valve, the incidence of pre-existing valvular disease was low (27 per cent), and only one of the 26 patients with right-sided endocarditis was known to have a previously abnormal valve.<sup>21</sup> The clinical picture is dominated by repeated episodes of septic pulmonary infarction owing to detachment of infected tricuspid vegetations, with *Staph. aureus*, candida, and pseudomonas as conspicuous offenders.<sup>86, 88</sup>

Signs of tricuspid valve dysfunction (i.e., the murmur of regurgitation) may be absent or minimal.<sup>21</sup> Major systemic emboli are not uncommon when the aortic valve is involved.<sup>17</sup> The pulmonary valve may be the sole site of involvement.<sup>70</sup>

More resistant pathogens are responsible when infective endocarditis follows the intravenous use of illicit drugs, but the etiologic agents differ somewhat in various centers. Among 28 cases encountered in 2 years at the Bronx Municipal Hospital Center, staphylococci accounted for 68 per cent and streptococci for 14 per cent, with only a single case caused by candida.<sup>25</sup> An acute course was characteristic (17 of 28 episodes were diagnosed within a week of onset), and right-sided cardiac involvement, primarily of the tricuspid valve, was present in 25 per cent. Neurologic manifestations were present in 50 per cent and 3 patients had severe unilateral purulent panophthalmitis. Aortic and mitral valve involvement far exceeded tricuspid valve involvement in an autopsy series, also from New York, in which 20 per cent of the cases were due to gram-negative bacilli.<sup>17</sup> These authors initially suggested a bias favoring candida endocarditis in the reported literature, since they found only 3 such cases out of 36 they surveyed, but they then noted a sudden increase of candida endocarditis (4 successive cases reported by the medical examiner) over a period of a few months.

Solitary tricuspid valve involvement and septic pulmonary emboli

characterized almost half the 23 cases, all treated successfully, over an 18 month period at Cook County Hospital; pathogens recovered were primarily *Staph. aureus* (16 cases) or streptococci (2 *Str. viridans*, 3 *Str. fecalis*) but no candida species. Aggressive surgical and medical therapy saved 4 of 5 addicts with candida endocarditis seen at yet another New York hospital.<sup>16</sup> Four of the 5 had mixed bacterial (staphylococcal or streptococcal) and candidal infection (1 case each of *C. parakrusei*, *C. tropicalis*, and *C. stellatoidea*, and 2 cases of *C. krusei*) and recovered following prompt surgical exploration of the aortic, mitral, and tricuspid valves after just 5 to 10 days of amphotericin B therapy. This 80 per cent salvage rate stands in marked contrast to accumulated experience in the literature which reports that only 6 of 51 patients with candida endocarditis have survived, and mirrors the success of aggressive surgical therapy for candida endocarditis reported by others.<sup>3,4</sup> The polymicrobial character of infective endocarditis in patients using drugs is well recognized, with as many as four organisms—*Staph. aureus*, *E. coli*, *Str. fecalis*, and *B. fragilis*—involved simultaneously in one case.<sup>19</sup>

Polymicrobial infection was also noted in 5 of 21 patients with pseudomonas endocarditis related to intravenous heroin use seen in a 3 year period in the Detroit Medical Center.<sup>20</sup> Although *Staph. aureus* endocarditis remains prevalent among Detroit heroin mainliners, since 1969 *Ps. aeruginosa* has emerged as an important pathogen, more so than in any other reporting center. Local "cutting" and "filler" habits may be responsible for these recent experiences. Mortality among 9 patients treated only with antibiotics was 44 per cent, but survival did not correlate with serum bactericidal levels, since a titer even as high as 1:128, achieved in one case with tobramycin and carbenicillin, failed to prevent a relapse. Very early (average 5 days) institution of medical treatment appeared to favor survival. After medical failure, 13 patients underwent operation and 6 survived, primarily by the expedient of tricuspid valvectomy without valve replacement. The rationale behind this bold surgical approach was to continue further medical therapy free of a foreign body prosthesis and thereby permit possible healing of residual infection in the remaining portions of the tricuspid valve annulus. Each patient currently has controllable right ventricular failure and while intractable right-sided congestive heart failure is anticipated, prosthetic valves have not been inserted despite apparent bacteriologic cures because of continued intravenous use of heroin by these patients.

## EXPERIMENTAL ENDOCARDITIS

All infective endocarditis may derive from primary bland vegetations—nonbacterial thrombotic endocarditis.<sup>2,3</sup> These are interstitial, edematous valvular distortions with localized platelet vegetations, with or without fibrin, occasionally with collagen alteration and fibrinoid, consequent to many different forms of stress. Distorted valves are more susceptible to stress and more likely to develop nonbacterial thrombotic endocarditis. Surface bacterial contamination of these bland vegetations presumably transforms them into bacterial vegetations. Experimental

animal models have been difficult to standardize, but the recent introduction of a simple and reliable method for inducing bacterial endocarditis in rabbits has laid the groundwork for a series of elegant experiments that begin to unravel the pathogenesis and in vivo histology of this most interesting infection. By placing a plastic catheter into or at the entrance to either side of a rabbit's heart, sterile endocardial vegetations, mural and valvular, can be consistently produced.<sup>24</sup> Subsequent staphylococcal contamination of these catheters regularly yields bacterial vegetations.

Expanding on this model, investigators in England gave a single intravenous injection of *Str. viridans* to rabbits (not through the in situ catheters), hoping to simulate the clinical situation in which infective endocarditis follows a transient bacteremia while permitting exact timing of the onset of infection.<sup>27</sup> In rabbits with catheter-induced endocardial vegetations, streptococci showed a striking affinity for nonbacterial thrombotic endocarditis with bacterial counts comparable to those of reticuloendothelial organs such as liver and spleen, where capture of organisms is facilitated by slow blood flow, an abundance of phagocytes, and a network of cellular processes extending into the blood channels, none of which features apply to nonbacterial thrombotic endocarditis. Colonization occurs even if the catheter has been removed.<sup>29</sup> The most striking histologic event following induction of bacteremia, other than a paucity of phagocytes, was the abrupt appearance of a superficial layer of fibrin, at about 18 to 24 hours, which initiated continued vegetation enlargement while affording these bacterial colonies protection against circulating phagocytes. Within 48 hours most bacteria appeared to be in a resting phase.

In a companion study, metabolic activity of the bacterial vegetations was measured by their uptake of tritium-labeled L-alanine, a small, freely diffusible molecule which participates in intermediary metabolism and is also incorporated into subunits of the mucopeptide component of cell walls.<sup>28</sup> Autoradiographically labeled bacteria are presumably metabolically active and thus susceptible to penicillin, which inhibits the transpeptidase reaction assembling the cell wall. Heavily labeled colonies were usually near the surface, those with no label deep within the vegetation, and those with partial labeling in the intermediate zones, suggesting that the older, deeper colonies contained few metabolically active bacteria. The vegetations appeared to grow by surface accretion, with younger active colonies always near the surface.

The authors suggest a basic distinction between old and inactive deeper colonies and young, active surface colonies, with the latter the major target of antibiotics while the former are already dead or quiescent. In healing endocardial vegetations the surface fibrin layer is invaded by fibroblasts; antibiotics may act by reducing bacterial numbers in the colonies sufficient to permit fibroblastic invasion while the deeper colonies slowly sterilize themselves by aging and healing, but could serve as foci for relapse in the event of insufficient therapy. Single injections of candida, proteus, and staphylococci, but not a Cocksackie B<sub>1</sub> virus, or L-forms of a *Str. fecalis* strain also initiated infection of nonbacterial thrombotic endocarditis lesions in this model.<sup>29</sup>

Extending the study of this model to commonly recommended antibiotic prophylactic regimens, it was discovered that neither a single high dose of penicillin G, nor a low dose of benzathine penicillin given 30 minutes before the intravenous injection of *Str. viridans* prevented bacterial colonization of nonbacterial thrombotic endocarditis vegetations in catheter-prepared rabbits.<sup>30</sup> Penicillin G or ampicillin, together with streptomycin, or a penicillin regimen that provided both an immediate high blood level and a sustained albeit lower blood level consistently prevented bacterial colonization of nonbacterial thrombotic endocarditis.

This is the first convincing evidence that antimicrobial prophylaxis is effective in preventing bacterial endocarditis: all previous studies have indirectly inferred that suppression of detectable bacteremia following dental procedures can be equated with the prevention of bacterial endocarditis, an assumption that has never been clinically tested. Thus, some currently recommended prophylactic regimens may be incorrect and only appear effective because of an inherently low rate of infection. Bacterial colonization of nonbacterial thrombotic endocarditis could be prevented by certain antibiotic schedules even in the presence of a foreign body (i.e., the polyethylene catheter). This has considerable practical significance in light of current usage of cardiac prostheses, pacemakers, and intravenous catheters.

## ENTEROCOCCAL ENDOCARDITIS

Enterococci are traditionally considered the most penicillin-resistant streptococci responsible for bacterial endocarditis. Therapy for enterococcal endocarditis is usually a combination of high-dose intravenous penicillin (20 to 40 million units per day) plus streptomycin (1 to 2 gm. per day), the "classic" clinical example of antibiotic synergy, although some patients respond to large doses of penicillin alone. It is most important that penicillin-sensitive group D streptococci not be mistaken for truly resistant enterococci. *Str. bovis* contains a group D antigen but is susceptible to penicillin and other drugs in a pattern similar to *Str. viridans*.<sup>50</sup> It hydrolyzes bile esculin, but will not grow in 6.5 per cent sodium chloride broth; reactions in commercial *Str. fecalis* (S-F) broth are inconsistent and may not detect the difference.<sup>33</sup> Since genitourinary and gastrointestinal antecedents are as common in *Str. bovis* endocarditis as in true *Str. fecalis* (enterococcal) endocarditis, but the prognosis far better and therapy much simpler when the former is involved, this non-enterococcal category of group D streptococcal endocarditis deserves separate recognition; as many as 20 per cent of currently labeled "enterococci" may be *Str. bovis*.<sup>33</sup> Penicillin-sensitive gram-positive organisms of the *Aerococcus*-*Pediococcus*-*Gaffkya* group may be confused with enterococci in a busy hospital laboratory.<sup>20</sup>

The mortality rate for *Str. fecalis* (enterococcal) endocarditis is disturbingly high, as much as 50 per cent in some series.<sup>62</sup> An 83 per cent cure rate was obtained among 36 patients in a large series recently reported from New York in which penicillin (or ampicillin) plus streptomycin was employed.<sup>66</sup> To improve upon less favorable results else-

where, other investigators have recently studied the kinetics of the synergistic reaction with penicillin-streptomycin and penicillin plus other aminoglycosides.<sup>18</sup> Not all enterococci demonstrate this synergistic effect, but tests to establish or predict synergy are cumbersome and difficult to perform. It was suggested that enterococci with high-grade resistance to streptomycin (6,000 to 50,000 micrograms per ml.) would not demonstrate synergy,<sup>105</sup> but others have not confirmed this observation.<sup>110</sup> Augmented *in vitro* synergistic activity with penicillin plus kanamycin or gentamicin forms the basis for recommending these combinations in preference to the combination of penicillin and streptomycin.<sup>48, 112</sup>

Therapeutic failure in enterococcal endocarditis, however, is usually not related to drug failure, but to complications such as congestive heart failure, emboli, ruptured aneurysms, vasculitis, and myocardial infarction.<sup>51</sup> Despite the fact that 40 per cent of enterococci do not demonstrate a synergistic effect when exposed *in vitro* to penicillin and streptomycin,<sup>112</sup> proper penicillin-streptomycin therapy is seldom associated with a bacteriologic relapse or failure unless a complication supervenes. Therefore the use of more toxic aminoglycosides, such as kanamycin and gentamicin, ought not be adopted without further clinical experiences.<sup>54, 66</sup> In patients allergic to penicillins, vancomycin plus streptomycin is currently recommended, since vancomycin alone is bacteriostatic *in vitro*.<sup>66, 67, 116</sup>

## SURGICAL THERAPY FOR INFECTIVE ENDOCARDITIS

From 10 to 15 per cent of patients with infective endocarditis are candidates for surgery, either because of refractory infections or for repair of sequelae of healed lesions. Other than prophylactic closure of a persistent patent ductus arteriosus or removal of an accessible mycotic aneurysm, or rarely an abscessed spleen, surgical considerations in infective endocarditis are relatively recent.<sup>6, 61</sup> Repair of acquired septal defects, perforated valves and ruptured chordae tendineae and prosthetic or homograft replacement of destroyed or deformed valves have become commonplace after an initial period of understandable surgical reluctance.<sup>6, 32, 117</sup>

The optimal time for surgical intervention remains uncertain in many instances, however. There is little argument that acute aortic valve insufficiency is the single most serious prognostic event in the course of infective endocarditis, but there is uncertainty as to the optimal timing for surgery, although all agree that intractable congestive heart failure requires immediate valve replacement, no matter how brief the period of prior antibiotic therapy.<sup>36</sup> Sudden death in 7 of 11 patients with mild heart failure associated with acute aortic insufficiency dramatizes the precarious status of these patients.

Most recently, aggressive surgical management has focused on patients with active infections, refractory to antibiotic control. In a most comprehensive review of this topic, 115 cases collected from literature were added to 24 cases personally managed at The University Hospitals in Seattle, Washington.<sup>68</sup> The authors attempted to separate active from

healed lesions, and to relate them to an etiologic category on the basis of blood and valve cultures as well as microscopic examination of the valves. From available and sometimes incomplete data, 105 cases were adjudged active and 34 healed at the time of surgery. Early and late mortality rates were 25 and 8.6 per cent, respectively, with an early mortality rate of 26.6 per cent in those patients operated on during active disease and 11.7 per cent early mortality rate in those operated on during the healed stages of infective endocarditis. Residual infection was not a major problem although 13 patients (10 per cent) had positive valve cultures. Organisms were seen microscopically in the excised valves of 23 patients, but only 2 had positive cultures although L-forms were not sought. Among 8 patients receiving treatment for 0 to 10 days, 6 valves contained organisms microscopically but these did not grow on culture; the specific organisms involved in the corresponding preoperative blood cultures were not tabulated. The major postoperative complication encountered was recurrent valvular regurgitation, seen in 25 per cent of the patients who left the operating room.

Emergency replacement of the aortic valve was carried out in 10 patients with severe and intractable heart failure who were referred from other centers following prolonged (average 48 days) but unsuccessful treatment.<sup>117</sup> It was difficult to ascertain how many infections were active. In 5 of the 10 cases circumstantial evidence was present, but only 2 patients had positive valve cultures. Seven of this group of 10 patients had mycotic aneurysms at some time during the course of their infection, a much higher frequency than usually encountered.

These authors stressed the importance of recognizing the syndrome of acute aortic regurgitation when congestive heart failure occurs in patients with bacterial endocarditis, since the well known peripheral signs of chronic regurgitation caused by a widened systemic pulse-pressure may not be present. Features aiding the recognition of this syndrome are a small heart and normal electrocardiogram in the presence of congestive heart failure and a distinctive premature closure of the mitral valve, which can be confirmed by ultrasound echocardiography.<sup>117</sup> Congestive heart failure by itself carries a poor prognosis but not always a fatal one.<sup>62</sup> Temporary or inadvertent intravenous fluid overloading is one reversible cause for congestive heart failure in certain patients. Although myocardial lesions are present in almost 90 per cent of fatal cases,<sup>\*</sup> they are not thought to contribute to heart failure; whether they play a role in nonfatal cases is uncertain.<sup>100, 107</sup>

In certain cases of right-sided valvular infective endocarditis, even when acute infection and resistant organisms are involved, if vegetations are limited to the cusp margins and do not involve the basal attachments to the annuli there is reasonable hope for successful surgical intervention.<sup>88</sup> On the other hand, endocarditis associated with a deformed mitral valve consequent to calcification of the annulus fibrosis is characterized by involvement at the base of the valve with extension into the calcified ring and adjacent myocardium, making a surgical cure unlikely, if not impossible.<sup>13</sup>

Several reports not reviewed by the Seattle group begin to analyze these anatomic features in a more meaningful prognostic fashion and

support the clinical impression of many investigators that, if necessary, surgery can be performed successfully after very brief periods of antibiotic treatment, particularly if the anatomic lesion is favorable. A convincing argument for early surgical intervention emerges from a carefully detailed report of 19 cases which listed the organism, nature of the preoperative antibiotic therapy, and the pathologic findings and operative procedure in each case; the survival rate (16 of 19 patients) was impressive in a series heavily represented with staphylococci, and there was no instance of postoperative perivalvular insufficiency.<sup>22</sup> These authors speculate that early intervention avoided the presence of fistulas and sinus of Valsalva aneurysms (which indeed were not encountered), and accounted for their excellent results, as did the absence of annular or septal abscesses.

Several days of intensive antibiotic therapy may "sterilize" the valve surface in terms of a surgical procedure and while the deeper vegetations may not be affected, surgery can be performed successfully if the infection involves primarily the valve cusps or leaflets and not its annular attachments. Infection of the aortic root wall at the base of the valve cusp may occur either as irregular friable mural vegetations or as ring abscesses, aneurysms, or fistulas. Satisfactory debridement is rarely possible with aortic ring abscesses without subsequent disruption of the aortic suture line, but cures have been recorded.<sup>47</sup> Ring abscesses occur less often in association with mitral valve vegetations.<sup>8</sup> Even in the presence of active infection, aneurysms of the aortic root have been successfully excised during aortic valve replacement.<sup>40</sup> Complete heart block may be associated with aortic valve involvement, by extension of the infection to the posterior (noncoronary) aortic sinus in proximity to the atrioventricular node and the bundle of His; cardiac pacing may permit an adequate period of antimicrobial therapy to be followed by successful valve surgery.<sup>109</sup> Indeed, it has recently been suggested that evolving intraventricular or atrioventricular conduction disturbances during the course of endocarditis indicate the presence of myocardial abscess or an aneurysm of the sinus of Valsalva, strong indications for prompt surgical intervention.<sup>51</sup>

Aggressive surgical management in the face of active, uncontrolled infection has been successful in patients infected with candida, pseudomonas, *Serratia marcescens* and other gram-negative pathogens, who are seldom salvageable by antibiotic therapy alone.<sup>1, 6, 11, 46, 53, 86</sup> Q fever endocarditis also qualifies for early surgical consideration because of the poor response to tetracycline,<sup>43</sup> especially in advanced cases.<sup>59</sup> Cerebral mycotic aneurysms in infective endocarditis often present with unilateral headache, focal neurologic signs, and "aseptic" cerebrospinal fluid or subarachnoid hemorrhage.<sup>119</sup> Prompt carotid angiography may hasten successful surgical excision.

The diagnosis and management of infected cardiac prostheses poses special problems. It is important to distinguish between early endocarditis resulting from contamination at the time of surgery and late endocarditis caused by transient bacteremias from urinary, dental, or other manipulations.<sup>21</sup> The former carries a fearsome prognosis, but the latter may be cured with antibiotics alone provided the prosthesis is well incorporated.<sup>24, 32, 99</sup>

Sande et al. analyzed 24 episodes of sustained bacteremia in 22 patients with prosthetic heart valves.<sup>11</sup> In the first group of 11 patients, 9 developed positive blood cultures 25 or more days after surgery (median 60 days) with gram-positive organisms (10/11), and no obvious source for the bacteremia. Ten developed new or changing murmurs late in their illness; all 11 had endocarditis and died, although most of the organisms recovered were sensitive to the prophylactic antibiotics used after surgery. In contrast, the second group of 13 developed bacteremia earlier (mean 12 days, 11 of 13 less than 25 days), 9 with gram-negative bacteria, and 12 had an obvious possible source for the bacteremia, such as pneumonia, sternal wounds, central venous catheters, suppurative phlebitis and infected pacemaker. Changing murmurs were not present; 7 of 13 survived with medical management alone and endocarditis was not present clinically or at autopsy in the 6 patients who died. A companion editorial pointed out that bacteremia developing shortly after implantation of a prosthetic valve cannot always be equated with infection of the prosthesis, but that none of these criteria (timing, nature of the organism, or even the presence of an obvious extracardiac focus of infection), singly or in combination, will always distinguish intracardiac from extracardiac infections.<sup>113</sup> Valvular colonization with or without evidence of endocarditis may occur with gram-negative bacilli, even *Pseudomonas cepacia*, but ultimately yield to effective antibiotic therapy.<sup>103</sup>

Experience with prosthetic valve endocarditis at the Massachusetts General Hospital differed from that reported by Sande's group.<sup>21</sup> Early postoperative gram-negative bacteremia was associated with prosthetic infection in 4 of 5 cases. In 19 cases of late endocarditis, the largest group thus far described, the bacteriologic spectrum more nearly resembled that of classical subacute bacterial endocarditis with a predominance of streptococci from oral or genitourinary sources and a favorable survival rate of 58 per cent in contrast to the mortality rate of 68 per cent among their early cases of endocarditis.

Reoperation in patients with infected prostheses, regardless of the organism involved, probably should not be delayed beyond the first relapse, even if active infection is present.<sup>113</sup> Involvement of the annulus may also preclude successful surgery in such patients.<sup>27</sup> Infection at the aortotomy site, rather than on the prosthesis, has been reported and should be suspected when auscultatory or radiologic evidence of valve dysfunction is absent in patients with cardiac prostheses and positive blood cultures.<sup>38</sup>

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## Bacteremia Caused by Gram-Negative Bacilli

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In the past four decades, bacteremia caused by opportunistic gram-negative bacilli has evolved from a relatively uncommon disorder to a major health problem throughout the world. The incidence continues to rise at an alarming rate, despite the availability of potent antimicrobial drugs. It is estimated that there now may be as many as 100,000 deaths caused by gram-negative bacillemia in the United States each year.<sup>59</sup> Recent evidence suggests that the clinical setting and relative frequency of organisms causing the condition may be changing.<sup>77</sup> Organisms that rarely caused infection in the past have emerged as significant pathogens. Intrahospital and nationwide epidemics of gram-negative bacillemia have occurred. New clinical syndromes, unusual portals of entry, and different mechanisms for development of bloodstream infections caused by those organisms have been documented. New information is available concerning immunologic protective mechanisms against gram-negative infections. The purpose of this report is to review briefly, in view of current developments, selected aspects of the problem of bacteremia caused by opportunistic gram-negative bacilli.

### CAUSATIVE ORGANISMS

Although *Escherichia coli* has generally been the most common pathogen responsible for gram-negative bacteremia, members of the Klebsiella-Enterobacter-Serratia group have become the most frequent causes of the condition at some large medical centers.<sup>77</sup> Dupont and Spink<sup>25</sup> noted that the incidence of bacteremia caused by members of that group increased steadily in recent years, whereas the incidence of bacteremia caused by *E. coli* remained relatively constant. Several inves-

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tigators have documented the rising incidence of septicemia caused by *Serratia marcescens*,<sup>2, 9</sup> an organism not generally regarded as a pathogen until recently.<sup>21, 23, 100</sup> Data now available from some large hospitals indicate that the incidence of bacteremia caused by *Pseudomonas aeruginosa*<sup>30, 99</sup> and by *Proteus*<sup>1</sup> is also increasing. Recent reports attest to the frequency and high mortality from polymicrobial bacteremia;<sup>8, 39, 40</sup> gram-negative bacilli are the organisms most frequently involved in such infections. Before 1960, bacteremia caused by members of the Bacteroidaceae was diagnosed infrequently,<sup>66</sup> but in the past decade, the Bacteroidaceae have been shown to be a common cause of bacteremia.<sup>17, 68</sup> This may be due in large part to improved techniques for isolation of anaerobes.<sup>17</sup> Currently, Bacteroidaceae account for 9 to 10 per cent of all positive blood cultures at some medical centers.<sup>17, 101</sup>

Among the less common opportunistic gram-negative bacilli recently identified in septicemias are species of *Pseudomonas* other than *aeruginosa*,<sup>33, 35, 82</sup> *Aeromonas hydrophilia*,<sup>22, 43</sup> members of the genus *Erwinia*,<sup>27, 73</sup> *Providencia* bacilli,<sup>42, 93</sup> *Edwardsiella tarda*,<sup>94</sup> *Hafnia alvei*,<sup>26</sup> *Bordetella bronchiseptica*,<sup>33</sup> and *Herellea* species.<sup>72</sup>

Those properties of opportunistic gram-negative bacilli which determine their ability to produce serious disease are not well defined. Some of the literature on this subject was reviewed in 1969<sup>90</sup> and will not be repeated here. Recently, Young and associates<sup>11, 103, 104</sup> showed that strains of *P. aeruginosa* and *A. hydrophilia* obtained from bacteremic patients were resistant to the bactericidal action of normal serum. Other workers demonstrated that strains of *E. coli* containing K antigen (envelope antigen) are more invasive than strains lacking this antigen.<sup>36</sup> This may be due to the inhibitory action of K antigens on phagocytosis and on killing of organisms by complement. Some strains of *S. marcescens* produce a proteinase capable of cleaving the third component of complement; it was postulated that this might contribute to the initiation or maintenance of an inflammatory response.<sup>11</sup> Other investigators<sup>74</sup> showed that strains of *S. marcescens* can survive and reproduce within leukocytes. Isolates of *Erwinia* and *Enterobacter cloacae* are able to persist and multiply in acidic solutions containing high concentrations of glucose, whereas most other organisms do not;<sup>27</sup> this appeared to be an important factor in the development of a nationwide epidemic of septicemias from contaminated intravenous solutions.

Several of the factors of *P. aeruginosa* responsible for pathogenicity have been described by Liu and associates.<sup>5, 51, 53</sup> Young<sup>103</sup> demonstrated that heat-stable somatic antigens of *P. aeruginosa* have properties enabling the organism to resist phagocytosis. The exotoxin of *P. aeruginosa* is capable of causing uncoupling of oxidative phosphorylation of susceptible cells.<sup>81</sup> Bacteroides organisms have several factors which may be related to pathogenicity.<sup>17</sup> These include endotoxin, heparinase, collagenase, fibrinolysin, and other proteolytic enzymes, as well as deoxyribonuclease and ribonuclease.

Endotoxins are lipopolysaccharides that form a portion of the cell wall of gram-negative bacteria. The endotoxins of gram-negative bacilli appear to be both antigenic and toxic, and produce a wide variety of biologic effects when injected into experimental animals. Some of the ab-

normalities produced by bacterial endotoxins in animals have been observed in patients with gram-negative bacilleemia. These include fever, hypotension, shock, consumption of complement,<sup>55</sup> activation of the kallikrein system and decreases in Hageman factor,<sup>70</sup> hyperlipidemia,<sup>32, 49</sup> elevation of degradation products of fibrinogen and fibrin,<sup>48</sup> and lesions resembling the generalized Schwartzman reaction.<sup>84</sup> Bacterial endotoxin may produce disseminated intravascular coagulation in animals, and disseminated intravascular coagulation has also been documented in some cases of gram-negative bacilleemia in humans.<sup>83</sup> A section of the kidney from a patient with fatal gram-negative bacilleemia and disseminated intravascular coagulation is shown in Figure 1. Braude and associates<sup>10</sup> recently made the interesting observation that antiserum to bacterial endotoxin prevents the development of disseminated intravascular coagulation in experimental animals.

Although bacterial endotoxin has long been suspected of being a major factor in the pathogenesis and manifestations of gram-negative bacilleemia, proof of this hypothesis is lacking. One of the major problems has been the lack of a specific, sensitive assay for bacterial endotoxin in body fluids.

Levin and associates<sup>50</sup> recently reported that endotoxin in low concentrations caused gelation of a lysate of the blood cells (amebocytes) of the horseshoe crab, *Limulus*. This led to the development of an assay capable of detecting minute amounts of endotoxin in human blood. Levin and associates<sup>49, 50</sup> found a good correlation between positive *Limulus* tests and infections due to gram-negative organisms. Patients with infec-

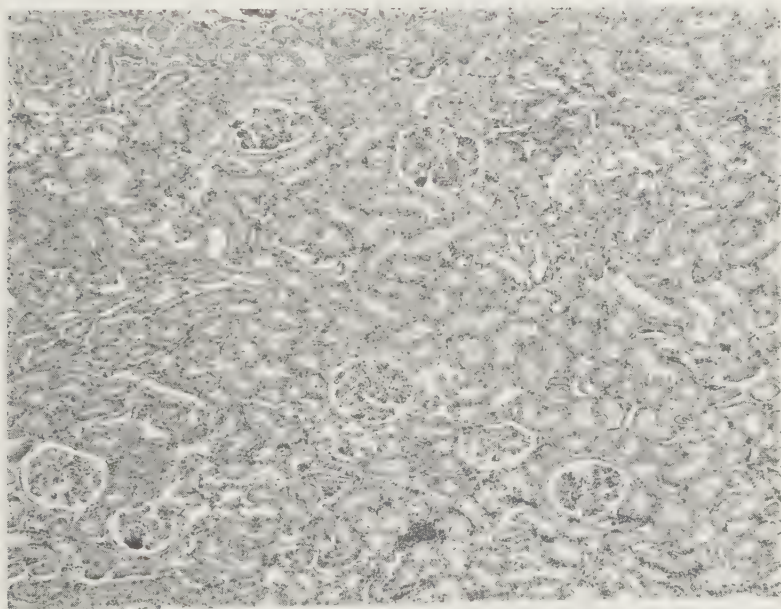


Figure 1. Photomicrograph of glomerular capillary thrombi in kidney of patient who had fatal disseminated intravascular coagulation associated with gram-negative bacilleemia. Hematoxylin and eosin stain,  $\times 64$ .

tions caused by gram-positive cocci had negative results. Hypotension and death occurred twice as frequently in patients with positive Limulus tests compared with patients with gram-negative bacteremia and negative Limulus tests. They suggested that the Limulus test could be used prognostically to define a population with high mortality, and possibly to assist the physician in distinguishing between gram-negative and gram-positive sepsis.

Unfortunately, Stumacher and associates<sup>66</sup> could not confirm these findings. Their Limulus assay system was hampered by both false-positive and false-negative results. The occurrence of shock or fatal outcome in gram-negative bacteremia failed to correlate with this assay for endotoxin. Further studies are urgently needed to resolve these discrepancies.

Lüderitz and associates<sup>74</sup> have reported that the cell walls of most gram-negative bacteria have almost identical lipopolysaccharide core structures, consisting of lipid A and ketodeoxycytionate to which differing O-specific oligosaccharides are attached. Active and passive immunization of animals with this core lipopolysaccharide from a gram-negative bacillus protects them from death after challenge with heterologous strains of gram-negative bacilli.<sup>15, 56</sup> Furthermore, McCabe and associates<sup>59</sup> showed that both shock and death in patients with gram-negative bacillemia were significantly less among patients with high titers of antibody to the core lipopolysaccharide (cross-reactive antibody) than in the group of gram-negative bacteremic patients with low titers of cross-reactive antibody. These studies may provide a basis for an immunologic approach to the prevention of gram-negative bacillemia.<sup>87</sup>

## PORTAL OF ENTRY AND PATHOGENESIS: SELECTED ASPECTS

In the preantimicrobial era, the usual sources of bacteremia due to gram-negative bacilli were the genitourinary tract, gastrointestinal tract, and biliary passages.<sup>28</sup> In recent years, other portals of entry have become relatively common including the skin (third degree burns), subcutaneous tissues (postoperative wounds), and lungs (Fig. 2).

According to Finland and Barnes,<sup>29</sup> the incidence of fatal endocarditis caused by gram-negative bacilli appears to be increasing; reviews of this condition have recently been reported.<sup>71, 78, 85</sup> Even more striking has been the high incidence of bacillemia associated with intravenous cannulas.<sup>64, 77</sup> Bacteremia caused by gram-negative bacilli has also been reported as a complication of infected arterial grafts<sup>20</sup> and arteriovenous fistulas.<sup>16</sup> Contaminated intravenous solutions recently have provided mechanisms for intrahospital and nationwide epidemics of septicemia caused by gram-negative bacilli.<sup>13, 24, 27, 80, 98</sup> The clinical course of a patient who had *Enterobacter* bacteremia secondary to a contaminated intravenous solution is shown in Figure 3. Gram-negative bacillemia has also been one of the expressions of intrahospital outbreaks of infections associated with contaminated respiratory therapy equipment.<sup>61</sup>

Data now available indicate that gram-negative bacillemia occurs frequently after surgical or instrumental procedures on the biliary, gas-

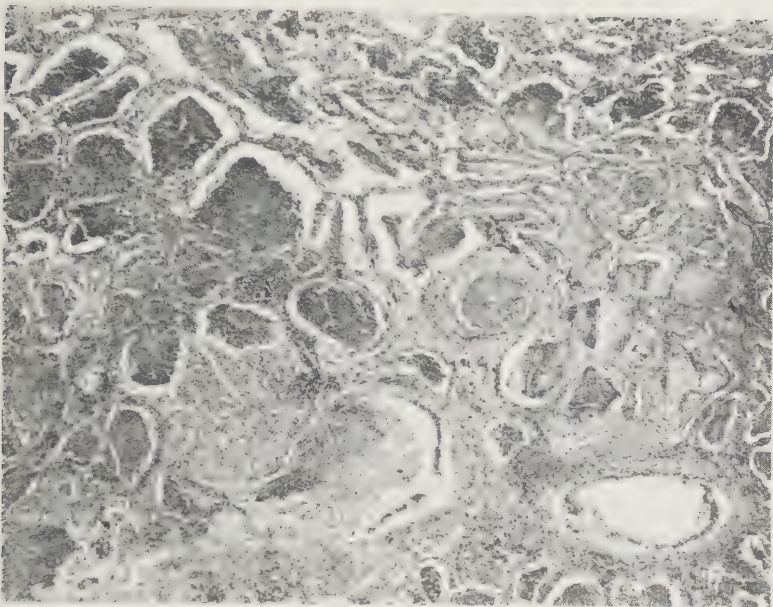


Figure 2. Necrotizing gram-negative bacillary pneumonia which was the apparent source of *Klebsiella* bacteremia. Hematoxylin and eosin stain,  $\times 40$ .

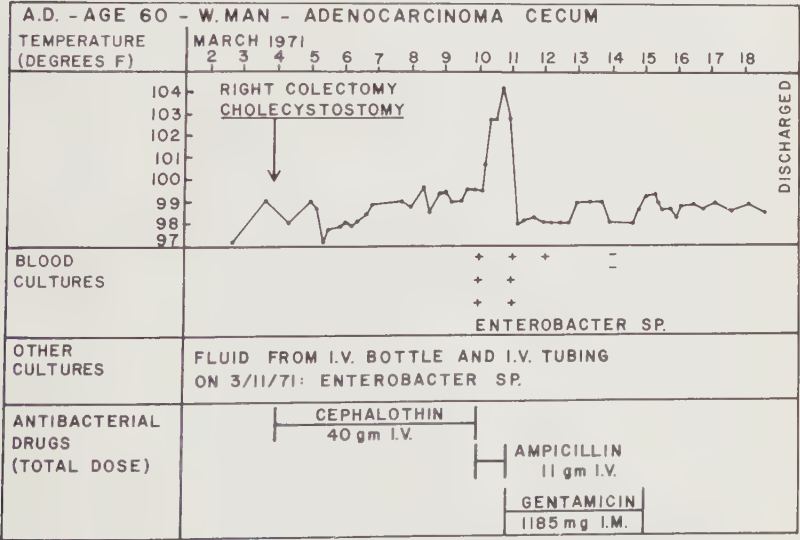


Figure 3. Graphic representation of clinical course of patient who recovered from gram-negative bacillemia secondary to a contaminated intravenous infusion.

trointestinal, or genitourinary tracts.<sup>12, 65, 96</sup> It even may develop after routine sigmoidoscopy<sup>16</sup> or proctoscopic biopsy.<sup>15</sup> Gram-negative bacilleemia is also common after septic abortion.<sup>92</sup> Usually these bacteremias are transient and clinically insignificant, but they may have lethal complications. Patients with pre-existing urinary tract infections<sup>96</sup> or positive cultures of bile at surgery<sup>16</sup> appear to be at high risk for development of bacteremia after surgery or instrumentation of the region in question. Data have also been presented suggesting that, in the presence of severe granulocytopenia in patients with leukemia, lymphoma, or carcinomas, the recovery of *P. aeruginosa* in routine surveillance cultures (especially of the rectum) identifies patients who will probably contract bacteremia from those organisms.<sup>90</sup>

The pathogenesis of gram-negative bacilleemia in patients with underlying hematologic diseases differs considerably from the pathogenesis of the condition in patients with underlying nonhematologic diseases.<sup>62</sup> In patients with hematologic diseases (e.g., leukemia, malignant lymphoma, aplastic anemia), bacilleemia frequently develops without previous surgery or instrumentation. Among the major predisposing factors are profound leukopenia, mucosal ulcerations, administration of adrenal glucocorticoids, and cytotoxic chemotherapeutic agents.

The most frequent portals of entry for bacilleemia are the lungs or mucous membranes of the respiratory and gastrointestinal tracts. The lung of a patient with chronic lymphatic leukemia and aplastic anemia who died of fulminating bacteremic pneumonia caused by *P. aeruginosa* and *Diplococcus pneumoniae* is shown in Figure 4. Several bacillary vascular lesions of *P. aeruginosa* are evident in the section. Lesions giving rise to bacteremia in patients with hematologic disease often show evidence of necrosis and inflammation with a paucity of polymorphonuclear leukocytes.

In patients with underlying nonhematologic diseases, leukopenia is not common and lesions usually are suppurative. A section of the kidney of a patient with underlying nonhematologic disease who died of fulminating *E. coli* bacteremia secondary to acute suppurative pyelonephritis is shown in Figure 5. In patients with underlying nonhematologic diseases, the sources of gram-negative bacteremia are more frequently located in the genitourinary tract, peritoneal cavity, or biliary passages than in the lungs or mucosal surfaces. The location of the distributing foci of infection is often related to underlying local anatomic abnormalities (for example, obstruction of the urinary or biliary passages) and antecedent surgical or instrumental trauma.

Bacteremia caused by gram-negative bacilli appears to be a relatively frequent complication in patients with hepatic cirrhosis; it may develop as the result of spontaneous peritonitis<sup>19</sup> or may be secondary to infections of the urinary tract or biliary passages.<sup>69</sup> Gram-negative bacilleemia also appears to be a relatively common complication in recipients of renal transplants, and most commonly arises from foci of infection in and about the revised urinary tract.<sup>1, 17, 76</sup> Among the major predisposing factors are heavy immunosuppressive therapy, leukopenia, hypogammaglobulinemia, hyperglycemia, failure of the graft, and complications such as ureteral leakage or postoperative hematomas.

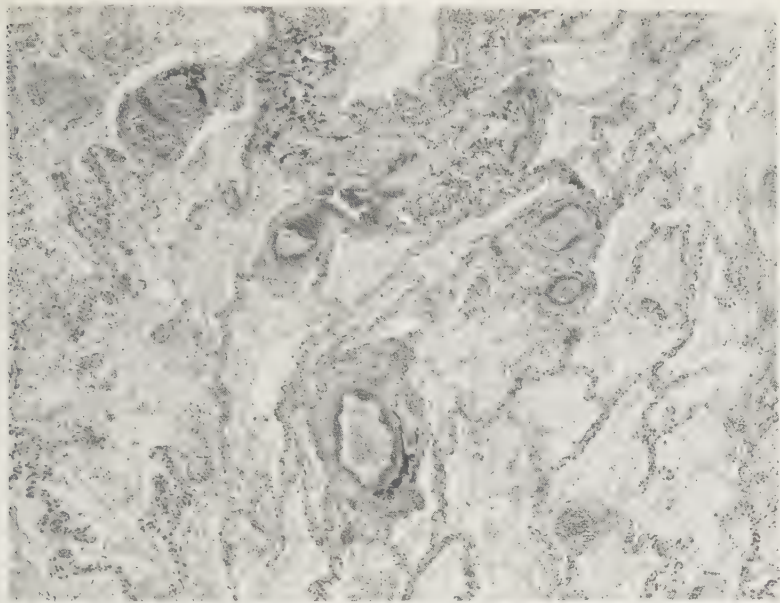


Figure 4. Photomicrograph of pseudomonas bacillary vasculitis in the lung. Hematoxylin and eosin stain,  $\times 64$ .



Figure 5. Acute suppurative pyelonephritis. Hematoxylin and eosin stain,  $\times 64$ .

Some investigators<sup>11, 31, 37</sup> have provided data indicating that the source of infection did not significantly influence the course of gram-negative bacillemia—no differences in mortality were observed in patients with various portals of entry when the severity of underlying non-infectious disease was taken into consideration by the method of McCabe and Jackson.<sup>57</sup> Other investigators<sup>34, 79, 80</sup> have found differences in mortality of gram-negative bacteremia with reference to the primary site of infection. Neeley and associates<sup>79</sup> found a lower mortality for patients in septic shock with infection arising in the urinary tract than for patients in septic shock caused by multiple intraabdominal abscesses or pneumonitis. Nishijima and colleagues<sup>80</sup> found a significantly higher mortality in patients who had gram-negative bacteremic shock from an enteric source of infection than in patients with a nonenteric primary site of infection.

Other workers<sup>17, 34</sup> have noted the relatively mild clinical course and low mortality in patients who had Bacteroidaceae bacteremia with septic abortion compared with patients with Bacteroidaceae bacteremia from extragenital foci of infection. This is probably attributable, in part, to the therapeutic efficacy of curettage and uterine evacuation in septic abortion.<sup>17</sup>

Recent experiences<sup>61</sup> suggest that septic endovascular lesions are often refractory to medical therapy and may be an important factor in the lethal outcome of cases of gram-negative bacillemia. Further study is needed to determine the influence of various portals of entry and of various lesions on the clinical behavior of gram-negative bacillemia.

## BACTEREMIA OF LONG DURATION

Investigators in the preantimicrobial era noted that bacteremia caused by opportunistic gram-negative bacilli was frequently of short duration and rarely lasted for more than 1 or 2 days.<sup>28</sup> In recent years, some investigators<sup>58, 89</sup> have emphasized the rapidly fatal course of gram-negative bacillemia especially in patients with lethal underlying noninfectious diseases. However, most studies of large numbers of cases of gram-negative bacillemia have been conducted retrospectively and duration of bacillemia either has not been determined or has not been reported. Members of our group<sup>63</sup> and Harris and Cobbs<sup>38</sup> recently documented the relatively high incidence of bacteremia of long duration among patients with bacillemia caused by opportunistic gram-negative bacilli. From 16 to 30 per cent of all patients with gram-negative bacillemia observed by the two groups had bacteremia of long duration lasting from 4 to 47 days. The large proportion of cases of bacteremia of long duration may have been influenced in part by factors related to requests for consultation with specialists in infectious diseases.<sup>38</sup> The average duration of bacillemia was 13.8 and 19 days in the two series respectively. Often the bacteremia persisted despite appropriate antimicrobial therapy and many of the patients had septic endovascular lesions. Figure 6 is a graphic representation of the clinical course of a patient who had gram-negative



## COMPLICATIONS

In 20 to 30 per cent of patients with gram-negative bacilleemia, a clinical syndrome of shock develops and the mortality ranges from 40 to 90 per cent.<sup>60</sup> The pathogenesis of this form of shock is incompletely understood and has been the subject of several recent reviews.<sup>18, 44, 60</sup> Increased attention has been focused on the possible role of immune mechanisms, pharmacologic mediators, vasoactive polypeptides, proteolytic enzymes, and the blood coagulation system.

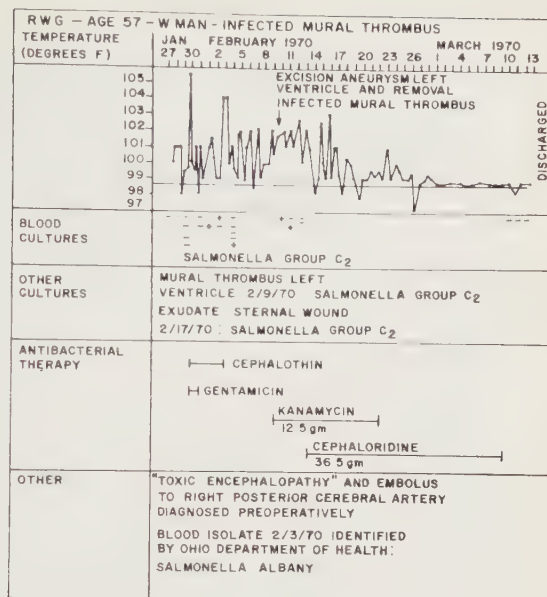
There is considerable controversy as to whether bacteremic shock is a discrete clinical syndrome with specific hemodynamic defects.<sup>80</sup> Some investigators found that the shock state is associated with a substantial reduction of cardiac output and elevated peripheral vascular resistance.<sup>80</sup> Others<sup>61, 75, 102</sup> observed that septic shock is associated with a high cardiac output and low peripheral vascular resistance. Despite the increased cardiac output, there appears to be defective oxygenation of tissues manifested by elevation of the oxygen content of mixed venous blood, decreased arteriovenous oxygen difference, and lacticacidemia. This defect in oxygenation may result from impaired tissue perfusion secondary to development of arteriovenous shunts which bypass the capillary exchange beds; or it may be caused by inability of the cells of some infected patients to utilize oxygen despite adequate tissue perfusion.

Nishijima and his colleagues<sup>80</sup> postulated that the variability of cardiac output in septic shock reported by various workers reflected the severity of the state of shock at the time the measurements were obtained. They reviewed the data from 159 cases of bacterial shock collected from seven medical centers, including their own, and demonstrated a remarkably high correlation between the initial value of cardiac index and outcome. The survival of patients who had a normal or elevated cardiac output was significantly better than that of patients in whom cardiac output was reduced.

Recent studies indicate that gastrointestinal bleeding<sup>3</sup> and respiratory insufficiency<sup>67, 91</sup> are common complications in patients with bacteremia caused by gram-negative bacilli. The pathogenesis of these complications is incompletely understood, but it is clear that they are important terminal mechanisms of death.<sup>62</sup>

## COMMENTS ON MANAGEMENT

Because of its broad range of activity, gentamicin appears to be the drug of first choice for the initial therapy of life-threatening bacteremia caused by aerobic gram-negative bacilli including *E. coli*, *Klebsiella-Enterobacter*, *Serratia*, *Proteus*, and *Pseudomonas*. However, gentamicin does not achieve high concentrations in bile,<sup>64</sup> and alternative drugs should be used when cholangitis is the source of bacteremia. Gentamicin alone is frequently incapable of curing *Pseudomonas* bacteremia in patients with severe neutropenia.<sup>7, 11, 61</sup> In this situation, a combination of carbenicillin and gentamicin appears useful; transfusions of granulocytes may also favorably affect the outcome.<sup>37</sup> Clindamycin and chloram-



It is extremely important to search for the source of bacteremia. In some instances, eradication of bacteremia depends upon removal of contaminated intravenous devices, extirpation of suppurative endovascular lesions, drainage of abscesses, or relief of visceral obstruction. Figure 8 is a graphic representation of the clinical course of a patient who required removal of an infected intramural thrombus of the heart for cure of a bacteremic infection caused by *Salmonella alban*.

It is equally important to obtain blood cultures repeatedly after initiation of antimicrobial therapy in order to recognize therapeutic failure at a time when the bacteremia is still amenable to medical or surgical treatment. Sometimes blood cultures remain positive even when signs of

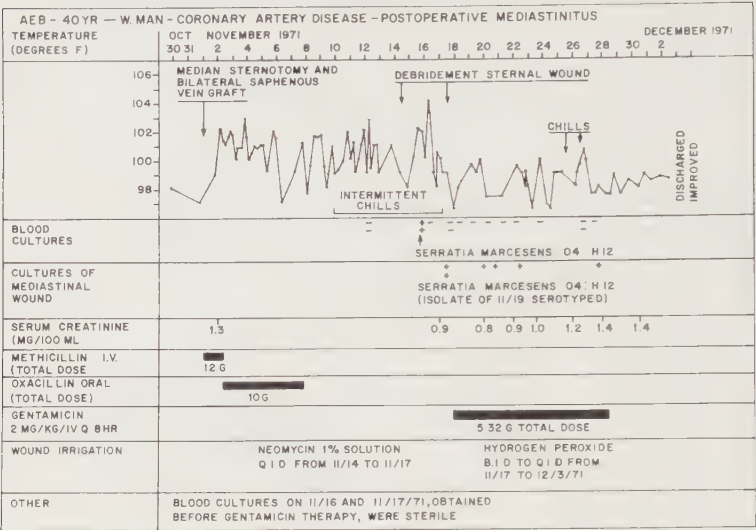


Figure 9. Graphic representation of clinical course of patient in whom bacteremia subsided before gentamicin therapy was initiated.

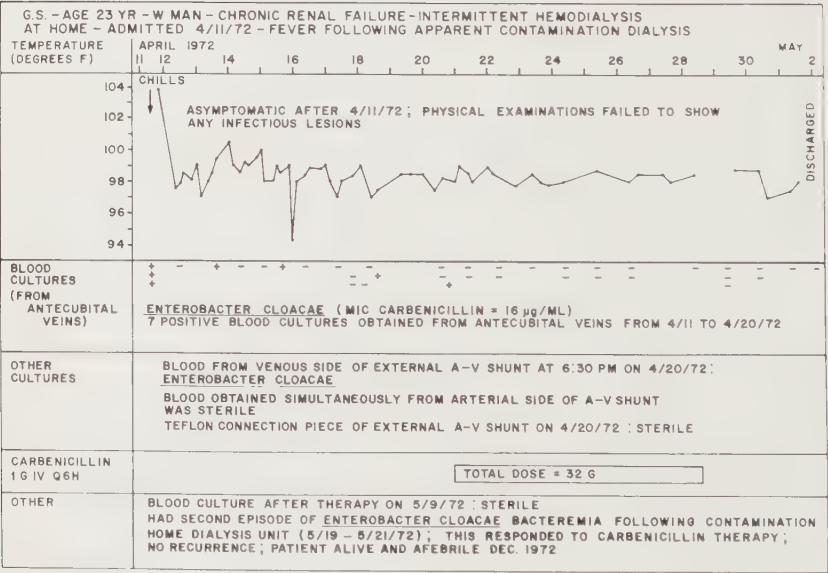


Figure 10. Graphic representation of clinical course of patient who became asymptomatic and afebrile despite persistent bacteremia.

clinical illness have diminished or subsided. Figure 10 shows the clinical course of a bacteremic patient who became afebrile and asymptomatic without therapy; however, bacteremia persisted intermittently until antimicrobial therapy was administered.

In treating patients with bacteremic shock, it is important to remember that hemodynamic derangements may vary among different patients with the same diagnosis or at different times in the same patient.<sup>60</sup> Appropriate therapy depends upon the type of hemodynamic derangement. Blood volume expansion is the keystone of management of the hypovolemic patient with septic shock.<sup>75</sup> Cardiac inotropic agents may be beneficial when shock results from a cardiac defect. The value of adrenal glucocorticoids in the management of bacteremic shock remains controversial.<sup>58, 60, 75, 80, 102</sup>

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## Nontuberculous Mycobacterial Infections of Man

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Although the disease that we now call tuberculosis was known in ancient times, it was not until 1882 that Robert Koch discovered the etiologic agent, *Mycobacterium tuberculosis*. By the turn of the century, bovine and avian tubercle bacilli had been described and by 1904 many other species of mycobacteria were recognized, such as Dubard's carp bacillus, Moeller's timothy grass bacillus, Friedmann's turtle bacillus, and Rabinowitsch's butter bacillus. Krause<sup>21</sup> in 1920 reviewed the current knowledge of the acid-fast bacilli that were widely distributed in nature. He divided them into three groups, the saprophytic or free-living bacilli, those associated with healthy animals or their products (bacilli in dung, milk, and butter), and those associated with tuberculosis-like disease of cold-blooded animals like turtles, fish, and snakes. He was able to document the existence of 40 different varieties of acid-fast bacilli exclusive of the tubercle bacillus. By 1925, tuberculosis had been defined as an infectious disease caused by "the tubercle bacillus."

There followed isolated reports of other mycobacteria apparently associated with human disease.<sup>4, 10, 17, 31</sup> The impetus for renewed interest in this subject was furnished by the papers of Buhler and Pollack<sup>3</sup> in 1953 and Timpe and Runyon<sup>17</sup> in 1954. Contributing factors were the widespread use of routine cultures of the sputum and the increasing proportion of patients infected with other mycobacteria, owing to the declining rate of tuberculosis infection. The reader is referred to the review articles by Runyon,<sup>33</sup> Lester,<sup>23</sup> Chapman,<sup>8</sup> and Fogan<sup>14</sup> for more complete documentation of the early literature.

### MYCOBACTERIA PATHOGENIC FOR MAN

The mycobacteria which are pathogenic or potentially pathogenic for man according to present knowledge are listed in Table 1. *M. avium* has been recognized for a long time as the avian tubercle bacillus, capable of

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Table 1. *Mycobacteria Pathogenic for Man*


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<i>M. tuberculosis</i>	}	Mammalian tubercle bacilli
<i>M. bovis</i>		
<i>M. avium</i> —Avian tubercle bacillus		
<i>M. leprae</i>		
<i>M. marinum</i>	}	Optimum temp. below 37°C.
<i>M. ulcerans</i>		
<i>M. xenopi</i>		
<i>M. szulgai</i>		
<i>M. fortuitum</i> — <i>chelonei</i> complex		
<i>M. kansasii</i> (Group I, photochromogen)		
<i>M. scrofulaceum</i> (Group II, scotochromogen)		
<i>M. intracellulare</i> (Group III, "Battey")		

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causing tuberculosis in fowl and occasionally in man. Identification of this organism mainly depended upon colony morphology, ability to grow well at 45° C., and virulence for chickens until Schaefer<sup>25</sup> and Marks et al.<sup>26</sup> showed that almost all avian strains were agglutinated by rabbit antiserum of serotype 1, 2, or 3. *M. intracellulare* strains are very similar to *M. avium*, differing mainly in nonvirulence for chickens and agglutination by other types of antiserum, but there are certain serotypes that seem to be intermediate forms retaining partial virulence for chickens. A certain proportion of cases considered to be examples of infection with *M. intracellulare* probably represents *M. avium* disease.<sup>12, 22, 43</sup> The organisms will be called *M. avium-intracellulare* in the remainder of this article.

*M. marinum* and *M. ulcerans* produce superficial lesions affecting the cooler parts of the body, no doubt because their optimum growth temperature is 30 to 33° C. *M. marinum* was recognized in 1926 as a cause of tuberculosis in fish.<sup>1</sup> The organism was rediscovered in 1954 as *M. balnei*. Its photochromogenicity, relatively rapid growth, and optimum growth temperature afford convenient markers for identification. A potentially severe ulcerating skin lesion known as the Buruli or Bairnsdale ulcer is the result of infection with *M. ulcerans*, which is very slow growing even at its optimum temperature. The disease has been seen mainly in Africa, Australia, Malaya, and Mexico.

The organisms previously known as the "atypical mycobacteria" are now classified into three principal species. *M. kansasii* is a slowly growing, photochromogenic bacillus whose colonies characteristically develop a sprinkling of red crystals of carotenoid pigment after prolonged exposure to light. It can sometimes be recognized in sputum smears by its large size and cross-banding of alternate well stained and unstained strips. *M. intracellulare* is also known as the "Battey bacillus." Its resemblance to *M. avium* has been mentioned above. *M. scrofulaceum* is a scotochromogenic species; the colonies are yellow to orange even when grown in the dark. It should be distinguished from the similar appearing *M. gordonae* (the "aquae" or tap water bacillus) which is commonly found in soil and water and is not associated with disease in man.

Those strains that grow rapidly on ordinary culture media usually can be classified in the group known as the *M. fortuitum* complex, which includes *M. abscessus*. It has been recommended that the latter species be divided and called *M. chelonae* subspecies *abscessus* and *M. chelonae* ss *chelonae*.<sup>39</sup>

Two relatively recent additions to the list of pathogenic mycobacteria are *M. xenopi* and *M. szulgai*. *M. xenopi* was first isolated from a toad in 1959 but it was not recognized as a cause of human disease until 1965.<sup>27</sup> Most of the cases have originated in England and the European continent but case reports from the United States are beginning to appear.<sup>11, 13</sup> The organism produces a scotochromogenic greenish-yellow pigment. It grows very well at 45° C., and the cells are long, thin, tapering, and branching. *M. szulgai* was first recognized as a species and a cause of human disease in 1973<sup>35</sup> although a strain had been isolated from human material at least 8 years previously.<sup>36</sup> The organism is scotochromogenic when grown at 37° C. but at lower temperatures the pigment is much more dependent upon light so that it would be classified as a photochromogen at 25° C. Cultures have been confused with *M. kansasii*, *M. gordonae*, and *M. flavescens* (a scotochromogenic rapid grower not known to be associated with disease).

### “SAPROPHYTIC” MYCOBACTERIA

These environmental strains are not associated with disease in man except in most unusual circumstances. Many of them, however, may be found in cultured material obtained from patients and it is therefore necessary to distinguish them from the potential pathogens. The rapidly growing species *M. phlei* and *M. smegmatis* are readily differentiated from the *M. fortuitum-chelonae* complex. *M. gordonae* is the slow growing scotochromogen which should be differentiated from *M. scrofulaceum* and *M. szulgai*. Among the previously designated Group III strains which must be separated from *M. avium-intracellulare* are three recognized species, *M. terrae*, *M. triviale*, and *M. gastri*.

### RELATIVE IMPORTANCE OF THE OTHER MYCOBACTERIAL INFECTIONS

For a reliable estimation of the proportion of mycobacterial disease attributable to these organisms it is necessary to distinguish disease-associated strains from those which appear in the sputum as casual or commensal organisms, or because of temporary colonization of the respiratory tract. The following figures are based on careful evaluation of our own material and of the published reports to include only cases of well-documented pulmonary disease in which these strains appear to be the etiologic agents. Expressed as the proportion of patients who have positive sputum cultures and who were admitted as suspected new cases of pulmonary tuberculosis, the incidence varies from one per cent as the

Table 2. Rates of Nontuberculous Mycobacterial Pulmonary Disease as Per Cent of New Cases with Positive Sputum Cultures, Cleveland Metropolitan General Hospital

YEAR	NO. OF CASES	TOTAL WITH POS. CULTURES	RATE
1963-1967	13	610	2.1%
1968-1970	6	358	1.7%
1971	5	135	3.7%
1972	7	135	5.2%
1973*	9	100	9.0%
<i>M. avium-intracellulare</i> .....			20%
<i>M. kansasii</i> .....			13%
<i>M. scrofulaceum</i> .....			4%
<i>M. xenopi</i> .....			1%
<i>M. szulgai</i> .....			1%
Unclassifiable**.....			1%

\*Through October.

\*\*Resembling *M. bovis* but not virulent for animals.

general overall figure to 16 per cent in one hospital in New Orleans. The incidence in Dallas and Houston, Texas, was reported to be 8 to 14 per cent and in Cook County in Illinois from 3 to 7 per cent. From Texas, Illinois and New Orleans, the majority of infections were caused by *M. kansasii* whereas *M. avium-intracellulare* was responsible for the 2 to 4 per cent incidence in the southeastern United States and in Australia. Our experience in Cleveland is outlined in Table 2, from which it may be seen that the proportion had remained unchanged at about 2 per cent for many years but has increased sharply in the last 3 years. There were no changes in laboratory personnel or techniques which could have accounted for this change. The infections were about equally divided between *M. kansasii* and *M. avium-intracellulare*.

## HUMAN DISEASE

### Pulmonary Disease

Lung disease is usually of the chronic granulomatous variety with thin-walled cavities, resembling pulmonary tuberculosis. Previous chronic lung disease such as silicosis, chronic obstructive lung disease, pulmonary fibrosis, and bronchiectasis has been noted in the majority of individuals who have *M. avium-intracellulare* infections but in only approximately half the patients who have *M. kansasii* disease. Many of the pathogenetic aspects have yet to be elucidated. Whether or not the disease usually represents a recrudescence of a dormant infection primarily acquired in the distant past or a newly acquired infection is not known. Occasionally the disease is seen in patients known to have had pulmonary tuberculosis previously and even more rarely, the two infections can coexist in an active form.

The results of treatment depend mainly on the mycobacterial species and its drug susceptibility pattern. Most *M. kansasii* strains are susceptible to rifampin and only slightly to moderately resistant to isoniazid, ethambutol, and streptomycin. With the use of triple drug therapy including rifampin for at least 2 years, the results should be almost as good as in the treatment of tuberculosis.<sup>21</sup> The *M. avium-intracellulare* strains, on the other hand, are usually quite resistant to each of the available anti-tuberculosis drugs.

Early results of routine drug treatment were poor with only 25 to 50 per cent early successes and a high relapse rate. Later experience with 4 to 6-drug regimens documented a 60 to 70 per cent early success rate which could be increased to 70 to 80 per cent with appropriately timed surgical treatment. Yeager and Raleigh's recent report on a series of 45 patients from one veteran's administration hospital from 1956 to 1971<sup>11</sup> showed that at 5 years of observation, half the patients were alive and well, 20 per cent had died with active disease, and the cumulative relapse rate was 20 per cent. In this series the treatment was variable, with half the patients receiving three drugs or less and 42 per cent having had adjunctive surgical treatment.

For the greatest chance of success it is recommended that drug treatment of *M. avium-intracellulare* disease should include at least four drugs, chosen from isoniazid, rifampin, ethambutol, ethionamide, and either streptomycin, capreomycin, or kanamycin. Resectional surgery should be done at the opportune time to remove cavities which have not closed, and drug treatment should be continued for as long as possible up to 2 years despite the many undesirable side effects associated with these intensive regimens.

There is much less information available on the proper drug treatment of pulmonary infections caused by the other mycobacteria. Pulmonary disease due to *M. scrofulaceum* is rare, but when it occurs it is difficult to control because the organisms are quite resistant to drugs. Treatment should be similar to that described for *M. avium-intracellulare* disease. We have reported four cases<sup>11</sup> and since then have seen three additional instances. Four of the patients were arc welders. One of them has been followed from the time 24 years ago when a routine chest film showed cavitory disease in the right upper lobe resembling pulmonary tuberculosis. An unsuccessful course of drug therapy and resection of the right upper lobe were followed by relentless slow progression of both cavitory and infiltrative disease on both sides and progressive loss of pulmonary function until the present state of respiratory insufficiency. During all this time his sputum has remained consistently positive for *M. scrofulaceum* and none of his children has become infected.

Disease from *M. xenopi* exhibits a variable response to drug treatment and the published drug sensitivity results are also not consistent. At least three drugs should be used depending on the in vitro test results. The few reported *M. szulgai* pulmonary infections have done relatively well on drug treatment; these strains are relatively, but not completely, susceptible to many drugs, especially rifampin. Pulmonary disease associated with the rapidly growing strains is rare and responds poorly to drug treatment.

## Lymphadenitis in Children

This is seen frequently by pediatricians and probably represents the most common manifestation of human nontuberculous mycobacterial disease. The magnitude of the problem gradually became known during the 10 years following the early reports.<sup>7, 32, 40</sup> It occurs almost exclusively in children most commonly at the age of 2 to 8 years and usually involves the lymph nodes of the anterior cervical area just below the mandible, especially at the angle of the jaw. Of the 59 cases seen at this hospital since 1959, 5 involved the inguinal nodes, 2 the epitrochlear nodes and 1 the mediastinal nodes. *M. scrofulaceum* was isolated from 35 of the 42 which were positive by culture and most of the others yielded *M. avium-intracellulare*.

An obvious site of inoculation in the form of splinters or other cutaneous injuries was found in most of the children with inguinal and epitrochlear nodes and it was assumed that a similar breach of the mucosa of the mouth or pharynx accounted for infection of the cervical lymph nodes. The disease must be differentiated from pyogenic and tuberculous lymphadenitis, from branchial cleft and hypoglossal duct cyst, and from lymphoma.

The children with mycobacterial adenitis usually appear healthy without evidence of fever, leukocytosis or previous sore throat. The nodes are not tender, there is no history of tuberculosis in the family, and the chest radiograms are negative. Tuberculin skin tests are usually quite characteristic and consist of little or no reaction to intermediate strength PPD, definitely positive second strength PPD reaction, and a stronger reaction to the PPD preparations made from *M. scrofulaceum* than those made from *M. tuberculosis*.

Total excision of the node is the treatment of choice and this usually is followed by complete healing and an insignificant scar. After the node has ruptured and drained, or after an incision and drainage procedure, it becomes much more difficult and sometimes impossible to do a clean excision and extensive scarring may result.

We have not found drug treatment to be of benefit and do not recommend its use under ordinary circumstances. The wounds have eventually healed completely in all these children and no late relapses have been noted even after many years of observation. The tuberculin skin tests have usually remained positive for many years.

## Superficial Infections Involving Skin and Subcutaneous Tissue

Swimming pool granuloma is the name of the skin disease caused by *M. marinum* infection. Many cases have been described including hundreds of children who acquired the infection by swimming in a contaminated pool.<sup>29</sup> Patients usually present with superficial abrasions around the elbows and knees which become ulcerated and crusted. Healing eventually takes place but the infection may persist for many months. Many children have been rendered tuberculin test positive as a result of swimming pool granuloma. Another type of superficial lesion is that which resembles sporotrichosis and is usually acquired by a minor injury which occurs in association with contaminated water, such as a

home aquarium. If drug treatment seems to be indicated for these relatively benign infections one may use a combination of ethambutol and rifampin to which most *M. marinum* strains are susceptible;<sup>31, 42</sup> they are usually resistant to isoniazid.

The Buruli or Bairnsdale ulcer can be a serious penetrating lesion leading to extensive tissue destruction. It responds poorly to drug therapy. Recommended modes of treatment are wide excision with skin grafting, and use of the heat cradle to provide temperatures unfavorable for the growth of *M. ulcerans*.<sup>16, 38</sup>

### Other Infections

Mycobacterial local abscess usually results from injections given with contaminated needles or through dirty skin and the organisms belong to the *M. fortuitum-chelonae* complex. Healing follows proper surgical drainage. Very few documented cases of urinary tract infection with *M. avium-intracellulare* or *M. xenopi* have been reported. Several cases of *M. kansasii* disease of the bones and joints are on record.

Widely disseminated, usually fatal infections may occur with any of these mycobacteria especially in association with hematologic abnormalities resembling leukemia and in immunosuppressed patients.<sup>18, 20, 45</sup> As in similar *M. tuberculosis* infections, it is sometimes impossible to determine which was the primary disease, the mycobacterial infection or the blood dyscrasia. The nontuberculous mycobacteria also must be added to the list of opportunistic pathogens that can cause disease in patients with renal failure during dialysis<sup>46</sup> and after kidney transplantation.<sup>15</sup> There are at least 2 reports of mycobacterial meningitis<sup>7, 30</sup> but neither case is well-documented. We have seen with Dr. Martin C. McHenry a patient on the hemodialysis program at the Cleveland Clinic who had meningitis due to *M. chelonae*. The organism was isolated from spinal fluid several times and the patient eventually succumbed to the uncontrollable infection. The response to treatment of these less common manifestations of mycobacterial disease is variable, depending upon the infecting organism and the underlying condition.

## EPIDEMIOLOGY

Information on the epidemiology of the other mycobacterial infections is accumulating slowly but is far from complete. The United States Public Health Service studies on Navy recruits indicated that, based on the results of skin tests with various tuberculin preparations, sensitization to PPD-G (made from a strain of *M. scrofulaceum*) and to PPD-B (made from a strain of *M. intracellulare*) was very common. Transmission of infection from person to person as indicated by secondary cases in families and other close contacts does not ordinarily occur. The situation is similar to the one which obtains in histoplasmosis, that is, there is a high infection rate in certain locations, overt disease is relatively rare, and the organisms are present in the soil. Some of these mycobacterial species are easily cultured from soil and water, some are found in animals or

Table 3. *Epidemiology and Clinical Characteristics of Mycobacterial Lung Disease*

MYCOBACTERIUM	PRIOR LUNG DISEASE	RESPONSE TO DRUGS	NATURAL HABITAT	USUAL SOURCE OF INFECTION
<i>M. tuberculosis</i>	—	good	man	man
<i>M. avium-intracellulare</i>	+	poor	animals, soil, dust	animals and environment
<i>M. kansasii</i>	±	good	? (rarely found in water and animals)	?
<i>M. xenopi</i>	±	variable	? (rarely found in water and animals)	?
<i>M. szulgai</i>	±	good	?	?
<i>M. scrofulaceum</i>	+	poor	water and soil	environment
<i>M. fortuitum-chelonei</i>	+	poor	soil and dust	environment

animal products such as milk. Available information regarding epidemiology is summarized in Table 3.

The natural history of *M. kansasii* infections remains a mystery. The organism has not been found in the soil and only rarely in water;<sup>2</sup> we have yet to identify it in any of the water samples we have tested. It has been cultured from raw milk,<sup>9</sup> but proper pasteurization should prevent infection by this route. *M. xenopi* has been isolated from water in England<sup>6</sup> but it has not turned up in any of our samples. Large outbreaks of *M. xenopi* infection or contamination have been encountered in at least two institutions, where the organism has been cultured from a significant proportion of sputum and other human material as well as from several environmental sources. All isolations of *M. szulgai* so far have come from human material and in association with disease. The *M. fortuitum-chelonei* complex is commonly found in the soil and dust and it is not difficult to appreciate how contamination might take place with these organisms of relatively low pathogenic potential.

The natural habitat of *M. ulcerans* has not been found, but that of *M. marinum* is known to be fish, with subsequent contamination of both fresh and salt water. Proper chlorination of swimming pools should eliminate them as a source of infection. The sporotrichoid variety of disease is usually related to contaminated home aquariums<sup>12</sup> or trauma associated with the handling of fish.<sup>19, 28</sup>

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## Infections Associated with Immunologic Deficiency Diseases

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Efforts to understand why a young patient had repeated infections with common bacterial agents led eventually to our current understanding of the immune system. A brief review of the clinical and laboratory aspects of the major categories of *congenital* immune deficiency will provide the background for anticipating and managing infections in the patient with acquired immune deficiencies. First we will review the typical clinical and laboratory findings which should suggest that a patient may have one of the various forms of congenital immune deficiency, and then we will describe the patient with acquired immunodeficiency, the result of malignant disease or treatment with immunosuppressive agents or both. What kind of infection is such a patient likely to have, what is its course, and how can it be diagnosed and treated?

### CONGENITAL IMMUNE DEFICIENCY

#### **Bruton's Agammaglobulinemia**

Bruton<sup>7</sup> in 1952 described an 8 year old boy who had been hospitalized 19 times for treatment of sepsis. During 10 of these illnesses, blood cultures were positive for pneumococci; types 33 and 6 were each responsible for 2 episodes. In addition, the child had repeated bouts of bacterial pneumonia, otitis, and cervical adenitis, all of which ran a prolonged course even with antibiotic therapy. Interestingly the child managed rubeola and varicella with no particular difficulty. The administration of polyvalent pneumococcal polysaccharide led neither to a decrease in the frequency of infections nor to the development of specific antipneumococcal antibody. An unusual plan of treatment was developed for this child: whenever he presented at the clinic with chills, fever and signs of infection, a blood culture was taken and penicillin was administered through the same needle. Eventually the child's serum proteins

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were studied and a deficiency of gamma globulin was demonstrated by electrophoresis. The child improved following treatment with periodic injections of pooled human gamma globulin and is alive and doing well today.

Patients with Bruton type of agammaglobulinemia, or sex-linked agammaglobulinemia as it is also called, lack the ability to make antibodies but have intact cell-mediated immunity. They have repeated infections with the common pyogenic bacteria, such as pneumococci, *Haemophilus influenzae*, streptococci, or pseudomonas, but can demonstrate delayed hypersensitivity reactions to intradermally placed antigens, are able to manage infections with viruses, fungi, and mycobacteria, and have normal graft rejection.

### Nezelof-DiGeorge Syndrome

Nezelof,<sup>21</sup> DiGeorge,<sup>12</sup> and others described patients with another form of congenital immunologic deficiency: normal serum immunoglobulins but a lack of cell-mediated immunity, severe lymphopenia, thymic hypoplasia or absence, and death following persistent infection with mycobacteria, viruses, or fungi.

### Swiss Type Agammaglobulinemia

Swiss authors, including Glanzmann,<sup>14</sup> Hitzig,<sup>16</sup> and others, collected a group of infants who appeared normal the first few weeks of life but then developed infections which disseminated and invariably led to death. Several of these patients were identified when they developed severe progressive disease following immunization with BCG or small-pox vaccine. Laboratory studies revealed both deficient immunoglobulin levels and defective cell-mediated immune responses.

## THE TWO-COMPONENT IMMUNE SYSTEM

Further studies based on patients with congenital abnormalities of the immune system were similar to those cited, and were accompanied by many experiments in animals, in which the effect of manipulation of the immune system could be determined. Extirpation of the bursa of Fabricius, a collection of lymphoid tissue in the terminal gut of birds, resulted in a clinical syndrome that resembled Bruton's agammaglobulinemia, whereas neonatal thymectomy in rodents, chicks, or rabbits produced animals with the equivalent of the "Swiss type" of agammaglobulinemia.

All these studies together provided the basis for our current concept of the two component immune system. Normally cells in the bone marrow, stem cells, differentiate into thymus-dependent small lymphocytes (T cells), the mediators of cellular immunity, or into plasma cells (B cells) which become capable of synthesizing specific antibodies. In congenital forms of immunologic deficiency, stem cells with the ability to differentiate one way or both ways are lacking.

## ACQUIRED IMMUNE DEFICIENCY INFECTION

## Hodgkin's Disease, Other Lymphomas and Leukemias

Patients with lymphomas such as Hodgkin's disease, leukemia and other malignant disease may acquire immunologic deficiencies secondary to their disease or its treatment and have impaired ability to resist infection. Hodgkin's disease is perhaps the best studied of these conditions. The proportion with immune deficiency varies with the stage of disease, whether or not the patient has been treated with radiotherapy or chemotherapy, and the method of testing for cell-mediated immunity.

In a group of 103 *untreated* patients with Hodgkin's disease, Young et al.<sup>29</sup> reported 11.7 per cent with skin test anergy; none was in stage I, and only 26.6 per cent of patients with stage IV disease had no reaction to any of the 6 skin tests applied. Aisenberg,<sup>1</sup> in his recent review, showed similar relationships to stage of disease and type and duration of treatment, but found that 60 to 70 per cent of patients in stages II, III, and IV were anergic. Patients with other malignant diseases such as lymphosarcoma, reticulum cell sarcoma, and acute leukemia, although not as thoroughly studied, also showed involvement of the immune response and a high frequency of infections especially late in disease or following intensive treatment with cytotoxic agents.

Casazza,<sup>9</sup> in a review of the records of 139 patients with lymphoma who died at the National Institutes of Health, reported that 25 per cent had no infections through the course of their illness; the other 75 per cent had an average of 1.3 episodes per patient. The majority of infections were due to common bacterial agents, although viral, fungal, mycobacterial or mixed etiology accounted for 30 per cent of the infections in those with Hodgkin's disease.

The characteristic type of immune deficiency and relative kind and frequency of infection in patients with lymphomas and leukemia are summarized in Table 1.

## Homograft Recipients

Similarly, patients who receive homografts and those who receive immunosuppressive drugs for nonmalignant diseases (nephropathy,

**Table 1.** *Characteristic Immune Deficiency and Frequency of Infection in Patients with Lymphomas and Leukemia*

	ANTIBODY	"CELL"	INFLAMMATORY	INFECTION	
	SYNTHESIS	IMMUNITY	REACTION	BACTERIAL	VIRAL
Chronic lymphatic leukemia	++++ <sup>1</sup>	+	±	+++	+
Lymphosarcoma	++			+	±
Reticulum cell sarcoma	+			+	±
Acute leukemia	+	+	++++	++++	++
Chronic myeloid leukemia	0			±	±
Hodgkin's disease	+	++++		+	+++

<sup>1</sup>Severity of deficiency or frequency of infection indicated by scale of + to ++++.

Crohn's disease, systemic lupus erythematosus) have an increased risk of infection which varies with the kind, dose, and duration of their immunosuppressive therapy and the kind, dose, and duration of therapy with "prophylactic antibiotics."

## INFECTIONS IN THE IMMUNOSUPPRESSED PATIENT

### Early Experience

In the early days of transplant surgery, death of patients with overwhelming sepsis within the first 3 months postoperatively was common. During the 3 to 40 month follow-up of 111 patients who received renal transplants at the University of Colorado<sup>21</sup> between November 1962 and December 1965, 55 patients died and complete autopsy data were available on 51. Systemic mycotic infections with *Candida* were diagnosed at autopsy in 12, *Aspergillus* in 5, *Nocardia* in 2 and *Histoplasma* in one. In addition, 3 patients had mixed fungal infections. The lung was the site of involvement in 19, but 11 of these patients had evidence of infection in other organs as well. In 4 cases, all caused by *Candida*, infection was present only in the gastrointestinal tract. Sputum cultures obtained from 14 of 19 patients with pulmonary involvement revealed the infecting fungus in 6. Antemortem diagnosis and treatment of fungal infection occurred in only 2 patients. Concomitant bacterial infection—pneumonia or sepsis usually due to *pseudomonas*, *staphylococcus* or enteric bacteria—was present in 19 of the 23 patients. *Pneumocystis carinii* was present in the lungs of 5 cases and cytomegalovirus in 13.

### More Recent Experience

A marked diminution in the frequency of infection and infectious death in the immunosuppressed host since 1965 has been indicated by several studies, especially that by Anderson and collaborators,<sup>22</sup> again at the University of Colorado. They observed that 82 per cent of all infections sufficiently severe to be contributory to death, occurred in patients who received their kidney transplants prior to 1966. In a group of 194 renal transplant recipients treated from 1962 through 1968, all followed for a minimum of 18 months or until removal of the transplanted kidney or death, 20 per cent had no infectious complications, 35 per cent had an infection that caused or contributed to death, and the remaining 45 per cent had only nonfatal infections. Factors associated with infection leading to death were severe renal failure (and the accompanying use of high dose immunosuppressive therapy), high dose prednisone therapy, and the accompanying hyperglycemia and leukopenia. The majority of patients died with bacterial infections although some succumbed to disease caused by viral, fungal, or pneumocystis agents.

The Colorado experience was similar to that reported by Briggs<sup>3</sup> and others in Boston and Simmons<sup>26</sup> and collaborators from Minneapolis. The incidence of infection in allograft recipients was related to the amount of immunosuppression and most infections were bacterial in etiology. Among 8 episodes of life-threatening pneumonia reported by Briggs, 6

were due to bacteria, and in 2 cases, both interstitial in type, no definite etiology could be established. The authors were of the opinion that the infrequent use of antibiotics in their patients prior to the development of pneumonia was responsible for the high incidence of common pathogens. Each patient in this series was gravely ill; nevertheless, all but one recovered fully.

## MANAGEMENT OF INFECTION

### Common Infections

The development of fever in immunosuppressed patients requires prompt attention: Chest x-ray examination and appropriate cultures should be taken immediately. Antibiotics effective against the "most likely" etiologic agents should be started early; delay in therapy may markedly affect the prognosis. Temporary cessation of immune suppressive therapy and reduction of prednisone dose to minimum levels sufficient to handle the stress of infection may aid the patient in overcoming infection. Modifications in the therapeutic regimen must be made depending on further etiologic information, course, or change in x-rays. Infection is a grave threat to the immune-deficient patient, but prompt aggressive, rational management may be life saving.

### Less Common Infections

In the less frequent situations in which infection in the immune-suppressed individual is not due to a common bacterial agent and treatment with a rational combination of antibiotics is ineffective, the etiologic possibilities are innumerable, the diagnostic procedures are complex, and in many cases the forms of treatment are hazardous and of questionable effectiveness. Furthermore the signs and symptoms of various infectious syndromes may be most unusual and not lead one to the proper diagnosis.

A partial list of less common agents associated with infection in the immunologically compromised host includes *Coccidioides immitis*, giardia, atypical mycobacteria, poliovirus, *Listeria monocytogenes*, strongyloides, schistosomes, and so on. Some of the more frequently seen uncommon causes of infection will be discussed (see Table 2).

### Toxoplasmosis

Toxoplasma infection in the immune-suppressed patient with or without neoplasia is characterized typically by prolonged fever, peripheral lymphadenopathy, hepatosplenomegaly and less frequently enlargement of hilar or mediastinal nodes. However, central nervous system involvement\* with seizures, coma, obtundation, and hemiparesis is not uncommon. Diagnosis may be made by serologic studies or isolation of the organism by inoculation of mice. Toxoplasmosis in adults may be successfully treated with sulfadiazine, 4 gm. per day, and pyrimethamine, 25 mg. per day.

Table 2. Some Less Common Causes of Infection in the Immune-Deficient Patient

INFECTION	SYMPTOMS	DIAGNOSIS	TREATMENT
Toxoplasmosis	Prolonged fever; lymphadenopathy (hilar, peripheral); CNS; encephalitis	Isolation; serology (Sabin dye test or complement fixation test)	Sulfadiazine Pyrimethamine
<i>Pneumocystis carinii</i>	Interstitial pneumonia	Stain of sputum, bronchial brush, lung aspirate, lung biopsy	Pentamidine isethionate or sulfa and pyrimethamine
Aspergillosis	Pulmonary: Necrotizing broncho-pneumonia, infarction; (intra-cavitary fungus ball rare); Pulmonary and disseminated: Intestinal, CNS, renal, thrombosis, infarction, hemorrhage	Cultures often negative; mixed infection frequent	Amphotericin B
Candida	Mucocutaneous, disseminated; may be associated with other infections	Culture—smear	Amphotericin B
Herpes simplex	Mucocutaneous, GI, Pulmonary, CNS; Disseminated; not usually fatal	Isolation; antibody rise (neutralization test)	Idoxuridine; cytosine arabinoside
Herpes zoster—varicella	Local skin lesions; frequently disseminated; pulmonary, CNS	Appearance and distribution of rash; culture, serology (complement fixation test)	Zoster immune globulin (ZIG) prophylactically; idoxuridine
Cytomegalovirus	Inapparent infection; "CMV Mononucleosis;" fever, leukopenia, lymphocytosis; hepatitis; intestinal pneumonia	Antibody rise (complement fixation test); isolation; histology	Idoxuridine; cytosine arabinoside

## Pneumocystis

The prompt diagnosis and treatment of *Pneumocystis carinii* pneumonia in the patient with a "compromised" immune system generally leads to marked clinical improvement;<sup>13</sup> however, it is difficult to determine which patients with diffuse interstitial pneumonitis are infected with the pneumocystis organism. Examination of properly stained specimens of sputum for cysts are rarely positive. Percutaneous lung aspiration or preferably open lung biopsy appear to be the most reliable techniques for making a diagnosis, although bronchial washings may be positive in some cases. No serologic method is currently available. Treatment with pentamidine isethionate should be continued for a full 14 days unless precluded by an elevation of the blood urea nitrogen or hypoglycemia. Treatment with sulfadiazine, 4 gm. per day, and pyrimethamine, 25 mg. per day, is an acceptable therapeutic alternative. Patients with pneumocystis infection frequently have concomitant infections with bacteria, viruses, or fungi, and treatment with multiple agents may be required.

## Aspergillosis

Aspergillosis should be considered in the immunosuppressed host with progressive pulmonary infiltrates who does not respond to antibacterial therapy. Diagnosis is difficult to make and treatment is seldom effective. Among 93 patients with aspergillosis reported from the Memorial Sloan-Kettering Cancer Center,<sup>17</sup> 59 had antemortem fungal cultures and only 7 were positive. Amphotericin B was administered to 14 patients either because of a presumptive or culture-proved diagnosis. All these patients had malignant disease and the long-term survival was most closely related to the course of the primary disease rather than to treatment of the aspergillus infection. One patient with an aspergillus "fungus-ball" was treated by surgical excision with a good response.

## VIRUS INFECTIONS

Viral infection, particularly with herpes simplex virus, cytomegalovirus, and varicella-zoster, all members of the herpesvirus family, is relatively frequent in immunosuppressed patients. The course of a virus illness in such patients may be protracted or complicated by superinfection with bacterial or fungal agents, but is seldom fatal. Chemotherapy of viral infections is not of proved effectiveness and in many cases where treatment may have been indicated, the diagnosis is not made until late in the disease or at postmortem examination. The characteristics of infection with the more frequently occurring viral agents will be reviewed. Hopefully, early diagnosis and proper management will increase further the proportion of immunosuppressed patients surviving these infections.

## Herpes Simplex

Recurrences of herpes labialis were no more frequent following renal transplantation than before, among a group of 55 Danish patients<sup>28</sup> who

survived at least one month following surgery. In none of the first 60 patients who died following transplantation in Denver, was herpesvirus recovered at autopsy (cytomegalovirus was found in 30, Herpes zoster in 1).

In an attempt to determine the significance of Herpes simplex infection in one group of immunosuppressed subjects—those with hematologic malignancy—Muller<sup>18</sup> and collaborators reviewed the records of patients seen at the Mayo Clinic from 1960 through 1969. There were 20 patients with various hematologic malignancies and herpesvirus infection. No deaths were attributable to the herpetic infection. In 16 cases the lesions remained localized, in 3 there were crops of lesions involving several sites and in one patient there was a generalized varicelliform eruption from which herpesvirus was isolated.

Nash<sup>20</sup> found histologic evidence of herpetic infection in the esophagus and/or middle and lower respiratory tract in a large proportion of burned patients and cited reports in the literature describing similar findings in the immunosuppressed host. He suggested that the frequency of herpes simplex infection may be underestimated because of inadequate diagnostic procedures.

An uncommon but severe form of herpes infection involves the central nervous system. Price et al.<sup>21</sup> described a patient with Hodgkin's disease and impaired immunity in whom signs of a progressive encephalitis developed over a 7 week period, terminating in death. Clinical and laboratory findings were so atypical that even with 2 brain biopsies diagnosis was delayed until approximately 6 weeks after onset when it was made by the indirect hemagglutination method. This case illustrated the fact that in the immunosuppressed individual, herpesvirus may produce a bizarre, diffuse encephalitis quite unlike that seen in the individual with a normal immune system.

Thus, herpes simplex infection in the immunosuppressed patient may be underdiagnosed because of the unusual clinical manifestations produced—esophageal, respiratory tract, or central nervous system involvement rather than the more familiar and less serious mucocutaneous form.

### **Varicella-Zoster**

Varicella and herpes zoster represent different clinical manifestations of infection with the same agent. Varicella, a generalized disease, is seen in the young, susceptible host as the initial infection following which varicella-zoster virus may remain in a dormant form in dorsal root ganglia. Activation of this virus may be provoked by waning immunity, trauma, irradiation, or suppression of the immune system secondary to malignant disease, chemotherapy, or factors unknown. Virus replicated in cells of the dorsal root passes retrograde via sensory nerves to skin endings where the typical dermatome distribution of rash occurs. Normally the rash remains localized, but in some hosts, especially those with deficient immune systems, generalized, occasionally fatal disease may occur.

It is the impression of many physicians that herpes zoster occurs

with greater frequency among immunosuppressed populations but published reports do not support such a contention. The incidence of varicella-zoster disease among renal transplant patients, those with Hodgkin's or other hematologic neoplasms and normal persons over the age of 50 years is 8.2, 8.0, 7.9, and 9.1 per cent respectively.<sup>23</sup> The immunosuppressed patient, however, is more likely to have the generalized form of zoster and lesions apparently take longer to evolve and to heal. Despite this increased morbidity, serious complications are relatively uncommon and the varicella-zoster virus is not often implicated as the principal cause of death.

### Cytomegalovirus

Active cytomegalovirus infection can be established by virus isolation or serologic methods in over 50 per cent of renal transplant recipients and in a large proportion of patients with malignant disease. Most individuals in whom cytomegalovirus infection exists have no related symptoms, as is the case with the normal host. A syndrome resembling mononucleosis with fever, adenopathy, and atypical lymphocytes, but absence of heterophile antibody, has been reported by many investigators. The course is generally 1 to 3 weeks in duration and uncomplicated.

Craighead<sup>10</sup> recovered cytomegalovirus from the lungs of 12 of 16 renal allograft recipients. In 8 patients the infection was associated with histologically demonstrable inclusion-bearing pulmonary cells, but with frank pneumonia in only 2. It is difficult to determine the significance of the cytomegalovirus infection in 6 of these patients, the histologic changes were meager, and there had been no clinical evidence of pulmonary dysfunction.

Cytomegalovirus infection is apparently common in the immunosuppressed host. Some patients develop a mononucleosis syndrome 6 to 12 weeks post transplant. The occasional patient has pneumonia but most patients are asymptomatic.

### Measles, Vaccinia, and Other

Other viral infections occasionally produce severe or even fatal disease in the immunosuppressed host. Measles may result in an atypical giant cell virus pneumonia which can occur in the absence of the typical measles rash. Smallpox vaccination of the immunologically incompetent host may progress to vaccinia gangrenosa, generalized vaccinia and death. It is worthwhile to emphasize that the immune incompetent patient should receive *no live* vaccines: no smallpox, measles, rubella, or Sabin polio immunization.

Any debilitated patient, including the immunosuppressed, may be vulnerable to pneumonia and a severe illness with influenza virus infections. Attempts should be made to protect susceptible patients from exposure, if possible, and to immunize them with polyvalent influenza vaccine. (This is a *killed* virus vaccine.) Even if the immune response is not normal, there may be some protection produced.

## SUMMARY

The frequency of infection in the immunosuppressed patient—especially the transplant recipient—is decreasing but there is also a concurrent shift from a predominantly “common bacteria” etiology to a wide range of unusual agents and unusual clinical manifestations. In patients with malignant disease, infections are most likely to occur in the late stages when there is diffuse involvement by neoplastic cells and widespread toxicity from therapeutic agents. In the allograft recipient infection appears to be related to rejection phenomena and intensive immunosuppressive therapy. Minimal interference with the immune mechanisms of the host and the prompt initiation of appropriate diagnostic and therapeutic measures are the most effective ways to affect mortality from infection.

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## Diagnosis and Treatment of Systemic Mycoses

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Mycotic infections occur in a variety of clinical settings and range in severity from self-limited, nonsymptomatic processes to devastating, generalized fatal diseases. Although the reasons for this difference in course are not fully understood, empirical observations define two clinical situations: infection of a host with apparently normal immune mechanisms and infection of a host with suppressed immune mechanisms. A third situation is the hypersensitivity response to fungal antigens, but in this encounter proliferation of the fungus is not critical and the outcome of the encounter does not depend on the host's ability to contain the fungus. Therefore this is not the concern of this paper.

In the immunologically intact host several fungi found in the environment enter the body, usually through the lungs, proliferate, elicit an inflammatory response, disseminate, and are contained with no viability; are contained but remain viable; or produce progressive disease. In the latter two circumstances diagnosis is essential and treatment often mandatory. The following discussion will deal with diagnostic methods and treatment of the infections falling in this category.

### DIAGNOSTIC METHODS

Laboratory methods leading to a conclusive diagnosis can be divided into direct demonstration of the causative agent by culture or microscopy and indirect methods of demonstrating antibodies or antigens.

Culture remains the most conclusive demonstration of the presence of a microorganism, assuming that the laboratory is reliable. Culture on Sabouraud's glucose agar and its variations is most commonly used in the United States. Heavily contaminated source material (sputum, soil, feces) can be often decontaminated by injecting mice or hamsters in-

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traperitoneally with the suspension. After 4 weeks, the spleen and liver of the animals may be the source for pure cultures of the deep fungus. The animals manage to suppress the simultaneously injected saprophytic fungi and bacteria.

Biopsy is a rapid and often conclusive method of diagnosis, as are touch preparations from lymph nodes or lung, or smears from bone marrow, chest fluid, blood, etc. The Grocott methenamine silver stain is the outstanding empirical method of morphologic diagnosis. Fluorescent antibody stain, when available, is indeed the most specific method short of culture.<sup>32</sup> The mucicarmin stain is selectively positive with *Cryptococcus neoformans*, but not all cells become uniformly stained. The absolute need for well controlled special stains for the demonstration and identification of fungi especially in necrotic tissue cannot be overemphasized.

The interpretation of positive cultures or morphologic findings must be a combined clinical-laboratory venture. The presence of numerous organisms of *Histoplasma capsulatum* in a calcified lesion will obviously be less important clinically than finding even one such organism in an active lesion. Clinical and laboratory expertise and high-quality staining technique are indispensable, lest the laboratory becomes misleading rather than helpful.

Before discussing immunologic methods, the fact must be established that no purified or standardized antigens are commercially available for any of the procedures. The Center for Disease Control provides antigens for many State laboratories, so some semblance of standardization exists in this limited circle. Most university or community hospital laboratories use antigens of questionable quality, some probably very good, others not. Comparisons of results obtained with such heterogeneous materials are obviously inaccurate.

### Histoplasmin and Coccidioidin

Skin tests are excellent epidemiologic tools but of practically no diagnostic value in the sick patient, except in persons with previously known negative skin tests.<sup>12</sup> Since a positive skin test in histoplasmosis can produce a rise in titer of complement-fixing antibodies, a positive skin test may neutralize the usefulness of the complement fixation test as diagnostic of active infection for many months.<sup>33, 34</sup> Histoplasmin skin testing, therefore, should be eliminated as a "routine" diagnostic procedure. Blastomycin skin testing is of very limited value as indicated below.

Screening with indirect methods (complement fixation, precipitin, agar diffusion) can be extremely helpful and will often be acceptable circumstantial proof for the cause of a clinical picture in the absence of a positive culture or demonstration of the causative agent.<sup>12, 23</sup> A special situation exists in cryptococcosis where the excess of antigen neutralizes the circulatory antibodies, leaving detectable antigen in the spinal fluid or serum of the patient.<sup>2</sup> Antigen assay by the latex agglutination test may be positive in the face of negative mycologic findings, or negative antibody procedures (complement fixation indirect fluorescent antibody).<sup>9</sup>

Skin biopsies can be most helpful in view of the pseudoepithelioma-

tous reaction seen in blastomycosis (with regularity) and in coccidioidomycosis and sporotrichosis (occasionally). The thickened but mature squamous epithelium with intraepithelial microabscesses is so characteristic that it literally cries for special stains and demonstration of the etiologic fungal agent.<sup>46</sup> The dermal reaction may be granulomatous to suppurative, with variations in the degree of combination (epithelioid cell rims and central suppuration.) While *Blastomyces dermatitidis* and *Coccidioides immitis* as a rule can be easily identified, it is well to remember that *Sporotrichum schenckii* may be quite difficult to recognize and only rare *H. capsulatum* organisms may be present.

Each fungus has characteristics which are essential to know: the endosporulation in the spherules of *C. immitis*; the broad-based single bud arising from a thick-walled mother cell in *B. dermatitidis*; the intracellular (histiocytic) location, often in clumps, of uniformly small, round to ovoid, yeasts of *H. capsulatum*; the occasional presence of asteroid bodies with a central yeast in sporotrichosis.

Pulmonary biopsies show variable specificity, generally exhibiting a granulomatous response. It is, therefore, critical to demonstrate the agent. Certain patterns do suggest specific diseases.<sup>46</sup> Blastomycosis is characterized by epithelioid cell tubercles with central suppuration; coccidioidomycosis may have extensive caseation necrosis; sporotrichosis has scattered histiocytes in an otherwise nonspecific pneumonitis and histoplasmosis may show the entire gamut of the granulomatous reaction found in any of the other mycoses, tuberculosis or sarcoidosis.

Partially fibrous or hyalinized lesions may resist all attempts at making an etiologic diagnosis, and are considered inadequate material when obtained by biopsy. In contrast, caseated areas generally contain large numbers of organisms, as do calcified lesions.

Dividing biopsy specimens for culture and histology is essential in the approach to diagnosis. We recommend freezing the culture material until the microscopic tissue report becomes available, suggesting selective cultural procedures based on the suspicion aroused by the tissue reaction. On the other hand, the frozen material can be discarded if cancer is found histologically.

## HISTOPLASMOSIS

### Diagnosis

*Histoplasma capsulatum* is an organism found widely distributed in soil, but mainly in the mid-portion of the United States and in major river valleys in Canada, Venezuela, and other parts of the world. Millions of people are infected but never manifest clinically significant disease. Diagnosis is important in acute disseminated disease, in complications of primary infection or when chronic pulmonary disease or active extrapulmonary disease are present, because drug treatment is indicated.<sup>5, 8, 47, 50</sup> Diagnosis is also important to exclude other processes which would be erroneously treated. These include histoplasmosis, so-called "epidemic" histoplasmosis, self-limited primary disease, and complications of healed histoplasmosis involving mediastinal structures.<sup>8</sup>

**Table 1.** *Diagnostic Characteristics of Deep Fungus Infection*

	AGENT IN TISSUE	VISIBILITY IN TISSUES	TISSUE RESPONSE
Histoplasmosis	Histoplasma capsulatum; Emmonsia capsulata; Yeast oval 2-4 $\mu$ ; Intracellular (in groups)	Uniform size. In necrotic tissue special stains indispensable: (Grocott, Gridley, PAS, FAS). Mostly in histiocytes, most numerous in caseated areas	1. Hard tubercles—just nodules of epithelioid cells mimicking sarcoid. 2. Tubercles with caseation indistinguishable from TBC. 3. Calcified large lesions have numerous organisms in center of focus. 4. Scattered histiocytic groups in lymph nodes, liver, etc.
Blastomycosis	Blastomyces dermatitides; Ajellomyces dermatitides; 8-24 $\mu$ , round thick-walled yeast with single broad-based bud	Comparatively great variation in size. Sometimes in giant cells. Search without special stains can take a long time especially in skin lesions	From "typical" epithelioid cell tubercles with or without suppuration to large areas of necrosis. In skin, pseudo-epitheliomatous hyperplasia with intra-epithelial microabscesses. Organisms often seen in the microabscesses
Coccidioidomycosis	Coccidioides immitis; 10-240 $\mu$ , spherule with endospores; seldom arthrospores in cavities	Large size makes demonstration easy as a rule. Only endospore containing spherules are conclusive diagnostic cells. Well seen on H & E; better on Grocott, Gridley and PAS	Necrosis prominent feature of granulation tissue that otherwise shows all variations of epithelioid cell "tubercles"

**Table 1.** *Diagnostic Characteristics of Deep Fungus Infection (Continued)*

CULTURE	DANGER FOR LABORATORY PERSONNEL	SPECIAL CULTURE PROCEDURES	AUXILIARY (INDIRECT) LABORATORY METHODS
Lung most regarding in cavitary cases. Cultures from bone marrow, blood, lymph nodes and other biopsy material ideal since free of contaminants. 10-30 days, Sabouraud's dextrose agar	Moderate	A and B type. White and brown color. Induction of yeast form desirable for conclusive identification	Complement fixation test widely used; yeast phase especially helpful in screening and finding of active cases. Mycelial phase lower titer and often positive in chronic cases. Agar gel diffusion in some laboratories more specific than complement fixation test. Latex agglutination test simple but evaluation difficult. Skin test contraindicated as "routine" work-up
Lung slow growing; easily missed in sputum by overgrowth from saprophytes. Skin easily cultured from closed lesions. 10-40 days	Low	Slow growing colony changes easily to yeast phase at 37°C. on blood agar or cotton seed agar	Complement fixation much less convincing than in histoplasmosis and coccidioidomycosis. CDC claims good results with agar gel diffusion. Skin test not helpful except in acute pulmonary form, apparently
Dangerous especially outside endemic area (personnel not immune from natural infection). Autoclaving of culture does not destroy morphology of culture mount. Safe diagnostic procedure: intratesticular injection in guinea pigs, 3-10 days	High	Rapid growing colony with central "bald" area. Identification of barrel shaped arthrospores possible after autoclaving-desirable in view of extreme chances of laboratory infection	Complement fixation test very helpful; rising titer poor prognosis, falling titer opposite. Precipitin test becomes positive sooner, lasts shorter than complement fixation test. Skin test primarily an epidemiologic tool; will be useful in individual case only if previously negative result converts to positive. Positive skin test can precipitate erythema nodosum

*(Table continued on following page.)*

Table 1. *Diagnostic Characteristics of Deep Fungus Infection*  
(Continued)

	AGENT IN TISSUE	VISIBILITY IN TISSUE	TISSUE RESPONSE
Cryptococcosis	Cryptococcus neoformans; encapsulated yeast, +10 $\mu$ generally with single buds. pseudohyphae exceptional	Special stain with mucicarmine stains selectively. <i>C. neoformans</i> . "Holes" surrounding yeast cells characteristic	1. Cryptococcus colonies (almost) without tissue response. 2. Epithelioid cell granulomas with or without necrosis. 3. Mixture of histiocytes and polymorphonuclear response
Sporotrichosis	Sporothrix schenckii; rarely seen in tissues or exudate; small budding yeast	Difficult to demonstrate: FAS somewhat higher positivity than Grocott, Gridley, PAS. Not visible on H & E	Suppuration, histiocytic proliferation, rarely true granuloma (skin). Highly variable pulmonary reaction, including cavities
Aspergillosis	Aspergillus fumigatus; Seldom sporulates in tissues. Some authors diagnose disease from presence of dichotomic branching septate hyphae	Aspergillus fumigatus characteristic head with peripheral sterigmata bend upward. Long chains of spores from sterigmata. Head and spores seldom seen in tissues, but sometimes in bronchi, ear canal, pulmonary cavities	Nonspecific inflammation, rarely granulomatous, sometimes associated with ischemic areas of necrosis in lung
Candidiasis	Oval yeast cells, 2-5 $\mu$ with budding; when combined with pseudohyphae, diagnostic; yeasts alone not conclusive. Tissue invasion almost always by pseudohyphae	Candida albicans—principal pathogen of the genus. Ovoid yeast cells with generally single bud	Generally purulent lesions, rarely isolated granulomas. Abscesses common in parenchymatous organs in septicemia. Necrosis seen in burned skin, around infected heart valves, etc.

**Table 1.** *Diagnostic Characteristics of Deep Fungus Infection (Continued)*

CULTURE	DANGER FOR LABORATORY PERSONNEL	SPECIAL CULTURE PROCEDURES	AUXILIARY (INDIRECT) LABORATORY METHODS
Growth from spinal fluid satisfactory; sputum difficult. Assimilation tests necessary for identification from sputum. 24-72 hours	Low	Brown on thistle seed agar. Urease positive, growth at 37°C.	Serologic methods helpful in cases with few organisms. Latex agglutination detects free antigen in spinal fluid or blood. Sometimes positive in face of negative mycologic findings, negative indirect fluorescent antibody test and negative tube agglutination (the latter two measuring presence of antibodies). Latex test cross-reacts with rheumatoid factor. Skin test experimental
Easy growth from skin, 2-6 days. Sputum—numerous cultures necessary—easy in cavitory lesions	Low	White, waxy colony turns dark to black after a few days. Yeast phase easily induced at 37°C. and increased CO <sub>2</sub> tension	Complement fixation test workable but seldom used. Agglutination and agar gel diffusion in experimental stage, possibly promising. Skin test specific but value not established
Easily grown on most laboratory media. Fast growing white mold, fast turning into greenish dirty dark color. Ubiquitous presence of organism makes interpretation of pathogenic importance very difficult	Sensitization possible	Since <i>Aspergillus</i> grows much faster than other pathogenic fungi, suspicious colonies of <i>Aspergillus</i> should be cut off from the agar and subcultured on other media in order to allow slow growing pathogens to develop	Agar gel diffusion generally positive in pulmonary fungus ball and allergic aspergillosis. Similar results in complement fixation test. Skin test of little value except in allergic aspergillosis. Immunoelectrophoresis used in a few places, supposedly quite specific
Grows overnight on most laboratory media; white yeast like colony, rapidly identified with germ tube serum test (2 hr at 37°C.). Assimilation and fermentation slow way of speciation. Interpretation analogous to <i>Aspergillus</i>	Low	Several media with indicators in use, particularly in gynecologic offices. Fair number of errors possible if reliance on color change is exclusive criterion. Growth equally well at 20 and 37°C.	Precipitin and agglutination tests available in rare places. Value of serology undetermined or argumentative. Skin test not useful. Agglutination in healthy persons often positive (low titer). Precipitin reaction, if positive, suggestive of systemic candidiasis

The crucial factor in diagnosis is awareness of the broad clinical spectrum of histoplasmic infection. Any progressive inflammatory process of lung with or without cavitation must be considered as possible histoplasmosis. The clinical and roentgenographic resemblance to tuberculosis is striking, so that if mycobacteria are not recovered early in such a situation, *H. capsulatum* should be looked for. Even in established cavitary tuberculosis, histoplasmosis must be sought for since combination of the two infections occurs.<sup>22</sup> This also applies to the clinically and roentgenographically apparent primary complex (hazy infiltrate with enlarged hilar and/or paratracheal lymph glands). The picture may actually resemble an acute pneumonia which is slow to clear. Erythema nodosum, once considered unusual in primary histoplasmosis may be a valuable diagnostic sign.

In the "epidemic" case an acute flu-like illness associated with widespread, disseminated pulmonary infiltrates should be suspected as histoplasmosis if the history of exposure within 2 to 4 weeks to bird or bat excreta-contaminated soil can be elicited. In the case of the histoplasmosis, only identification of laminated circumferential calcification within the nodule(s) establishes the granulomatous nature and excludes malignancy. The development of mechanical mediastinal problems (superior vena cava obstruction, bronchial compression, broncholithiasis, esophageal traction diverticulum or with or without an esophageal-node fistula, etc.) in young people without evidence of malignancy elsewhere suggests old healed or healing histoplasmic infection.

Several diagnostic tools are available. Culture of the organism is the most conclusive but is useful only in chronic pulmonary or active disseminated disease. In the former, sputum is regularly positive when cultured on Sabouraud's medium or when injected into hamsters or mice, sometimes even on smear. In disseminated disease blood, bone marrow, biopsies of liver or lymph nodes are positive in addition to sputum. Mucosal ulcers may be seen in this situation and may also be positive on culture of biopsy. In acute primary pulmonary disease culture of sputum is rarely positive, but occasional positive blood and bone marrow cultures have been seen, especially in children. In all other forms of histoplasmosis, culture is negative with the exception of the epidemic case where the same conditions modify the likelihood of positive cultures as apply to acute primary pulmonary disease.

Demonstration of the organism by smear or biopsy is strong presumptive evidence of its presence but not necessarily of activity of the infection. In a clinically active situation demonstration of intracellular yeast cells in a tissue press of a mucosal ulcer using Wright's or Giemsa stain is highly suggestive. Confusion may exist, however, with phagocytosed candida species and leishmania organisms, so corroboration of the diagnosis by culture preferably or by serology must be sought. In biopsy specimens the use of stains that selectively stain the chitinous wall of the yeast cells (Grocott, Gridley, PAS) will reveal the organism much more frequently than routine study with only hematoxylin-eosin stain. Leishmania organisms do not stain with the Grocott procedure—a simple means of differentiation, since the kinetoplast may be hard to see in tissue sections. Again it must be emphasized that the finding of the organ-

ism is strong presumptive evidence that should be supported by culture or serology. Furthermore, determination of activity of the infection results from integration of histologic, cultural, serologic, and clinical observations.

Staining of tissues with fluorescent antibody has been studied, and though it is useful in noncalcified lesions, experience with calcified foci suggest no advantage over the simpler techniques such as the Grocott procedure. Use of the fluorescent antibody stain in handling sputum smears or blood smears does not seem worthwhile but experience is scanty.<sup>26</sup>

The serologic test used most widely in histoplasmosis is the complement fixation test. Titers are determined using mycelial phase (MP) and yeast phase (YP) antigens.<sup>12,23</sup> These represent the two biological forms assumed by this dimorphic organism. Mycelial phase titers of 1:8 or above or yeast phase titers of 1:16 or above indicate infection and are suggestive of activity of the process. Because change in titer is significant and because the higher the titer the more likely is the disease to be active, serial titers at 2 to 3 week intervals are indicated.

In spite of these general rules, the complement fixation titers are only useful when used in conjunction with clinical evaluation. Reasons for this include the occasional persistence of titers of 1:64 or above for up to a year after the primary infection heals, cross-reaction between antibodies specific for *H. capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*, clinical evidence of healing occurring before the titers drop, different forms of the disease having different patterns of serologic response, and the occasional rise in titers induced by a skin test with histoplasmin as noted above.<sup>33, 34</sup>

In acute primary symptomatic histoplasmosis both mycelial phase and yeast phase titers rise and fall in a matter of 6 to 12 weeks with the yeast phase usually being higher. In active disseminated disease titers with either or both antigens may be quite high, but not necessarily so, and they remain stable until effective treatment controls the progressive infection or death is impending, when the titers fall. In chronic granulomatous disease the titers may be high or modest (1:16 or 1:32) with both antigens, but again the yeast phase is generally the higher. With effective treatment titers may fall within a month or two or they may come down very slowly, persisting for more than a year. Epidemic cases behave like acute primary infections. All other infected persons have very low or no titers.

Of interest is that depressed cellular immunity, either iatrogenic or secondary to disease, does not seem to alter titers dramatically, although in selected cases titers may be suppressed. Diligent search for active disease is strongly indicated in any patient with immunosuppression in whom clinical evidence of infection is associated with even low titers of complement fixation antibodies.

Other serologic tests being used include the latex agglutination test and the gel diffusion test.<sup>12</sup> In both instances the mycelial phase antigen is used. Results up to this time suggest that these tests are most useful for screening. In the gel diffusion test, however, the H band shows considerable specificity, not influenced by previous skin testing. The M band

on the other hand is seen after a positive skin test. The M band alone has the same significance as a positive skin test—past or present infection. Studies have shown some correlation between the specific immune globulin moiety manifesting complement fixing specific antibody activity, but the technique is not yet practical for widespread use.<sup>1</sup>

### Treatment

In all cases in which infection with *H. capsulatum* is documented, evaluation of clinical type and activity of the process must be made. A fatal outcome is expected without drug treatment in chronic cavitary histoplasmosis, in meningitis, or in progressive disseminated disease.<sup>3, 37, 50</sup> Most other forms are self limited. The problem comes in recognizing the development of active dissemination or the change from an acute self-limited form of the infection to chronic cavitary disease. Therefore, when an acute primary pulmonary or epidemic case is encountered, careful clinical observation is necessary to document persistent fever and debility, leukopenia, hepatosplenomegaly, development of mucosal ulcerations or general body wasting as signs of progressive dissemination, or inexorable progression of cough and sputum, enlargement of pulmonary infiltrates, persistence of fever, sputum positive for *H. capsulatum*, and loss of vigor as signs of chronic pulmonary disease. In both of these clinical situations titers of complement-fixing antibodies remain at significant, sometimes rather high, or rising levels. In the very young (under 18 months of age) and in the immunosuppressed patient, dissemination is more likely, while in the man over 35 years of age, chronic pulmonary histoplasmosis is a greater threat.

Treatment in the three ominous situations noted above is with amphotericin B. This drug is toxic to kidney and, to a lesser extent, bone marrow, but in most patients all manifestations of toxicity disappear when treatment stops, provided that the total dose is under 3.0 gm. For disseminated infection a total dose in the adult of 1.0 to 1.5 gm. is adequate and for chronic pulmonary disease 1.5 to 2.0 gm. is recommended.<sup>3, 37</sup> In chronic pulmonary histoplasmosis, a total dose of 0.5 gm. has been tried but results are hard to interpret, so the higher dose is recommended. In children a total dose of 20 to 30 mg. per kg. of body weight for disseminated disease and 30 to 40 mg. per kg. for chronic pulmonary disease (rare in children) is recommended.

Administration of amphotericin B should begin with 5 to 10 mg., working up by daily increments to 50 mg., and then continuing treatment three times per week at that level; the total dose is given in 30 to 90 minutes, more slowly only in the rare person who cannot tolerate the rapid infusion; the infusion is followed with a flush of 30 to 50 ml. of 5 per cent glucose in water; a concentration of 0.1 mg. of drug per ml. of diluent (5 per cent glucose in water) should be maintained. The pH of the infusion should be kept above 5.5. Premedication (ASA, antihistamines, Compazine) for symptomatic treatment is used as needed. Fifteen to 50 mg. of hydrocortisone may be included in the infusion if chills and fever are a problem. Treatment may need to be withheld for a few days if the blood urea nitrogen level goes above 50 or if the serum potassium level falls below 3.0. Most important is to individualize the details of treatment for each patient.

End-points of treatment may be obscured by toxic effects of the drug, so conversion of sputum and improvement on chest x-ray examination in chronic pulmonary disease and healing of ulcers, shrinking of spleen and liver, and elevation of leukocyte count in disseminated disease are the only useful signs of improvement. Otherwise, when the planned total dose is achieved, treatment should be stopped and the patient observed.

No other drug is available at this time, although another, saramycin, was tested extensively, showed promise, but was then dropped. If chronic or disseminated histoplasmosis is found in combination with active tuberculosis, both diseases are treated as if the other were not present.

## NORTH AMERICAN BLASTOMYCOSIS

### Diagnosis

This infection is most often manifested clinically by characteristic skin lesions but it is an important pathogenetic concept that the infection is almost always a primary pulmonary one. The extrapulmonary manifestations, therefore, represent metastatic foci, and treatment directed against them alone overlooks the ominous presence of the pulmonary focus from which subsequent dissemination may take place.<sup>7</sup>

The characteristic skin lesions are grossly hyperplastic with centrifugal spread and central scarring. Microabscesses are frequently seen near the edges of these lesions and are excellent sources for pus from which culture will grow and 10 per cent potassium hydroxide mount will demonstrate *Blastomyces dermatitidis*. These lesions may be single or multiple, slow or rapid in growth, and may be predominantly hyperplastic or may demonstrate mainly suppuration, breakdown, ulceration, and sinus tract formation. Such lesions often begin as subcutaneous nodules with subsequent cutaneous progression.<sup>7, 10, 60, 65</sup>

Pulmonary blastomycosis is variable in character and may present as a typical primary complex with a parenchymal focus associated with hilar node enlargement; there may be multiple nodular lesions, confluent infiltrate and/or chronic cavitory disease; or there may be widespread disseminated alveolar and interstitial lesions. The clinical course may be explosive or indolent, or there may be few if any symptoms and a lesion seen on x-ray examination the only indication of illness.<sup>7, 10, 60, 65</sup> Conversely, chest x-ray lesions may not be easily identified although extrapulmonary lesions are seen.

Bone, joints, prostate, extrathoracic lymph nodes, and kidney may be involved as well as any other organ with the rarest site in the enteric canal from esophagus to anus. A combination of a pulmonary lesion with skin, bone, joint or prostatic foci should arouse suspicion of blastomycosis.<sup>7, 10, 65</sup>

The second epidemic of pulmonary blastomycosis recorded was only recently described.<sup>41, 56</sup> In both epidemics, explosive acute pneumonic disease was seen with apparent spontaneous recovery.<sup>49</sup>

Recovery of *B. dermatitidis* from pus, sputum, prostatic fluid, or biopsy material is done easily on Sabouraud's agar or on injection of mice

intraperitoneally. The organism is identifiable in 10 to 14 days but must be converted to yeast phase in animals or by appropriate *in vitro* techniques to differentiate it from *Paracoccidioides braziliensis*.

Demonstration of *B. dermatitidis* in pus, prostatic fluid, cerebrospinal fluid and sputum may be accomplished using 10 per cent potassium hydroxide. A few drops of the fluid are mixed with a few drops of the potassium hydroxide on a slide and are allowed to incubate for 20 minutes. This allows time for inflammatory and/or epithelial cells to be lysed. Microscopic examination under low or high dry power will then show the thick-walled, round yeast cell of 7 to 15 microns in diameter with a broad-based, single bud. These characteristics are highly specific for *B. dermatitidis* but should be corroborated by culture. A similar morphologic picture may be seen in histologic preparations using one of the special fungus stains, but again the characteristics should be corroborated by culture whenever possible.

Serologic and skin tests are of no value in North American blastomycosis except in the epidemic reported recently where the skin test was consistently positive in 36 to 48 hours. The complement fixation test was useless.<sup>41, 56</sup> These techniques have been used by many other investigators and the results are the same: a high percentage of false negative results in active cases and false positives, often in people known to be infected with *H. capsulatum*.<sup>10, 65</sup> Recently Kaufman has noted the diagnostic significance of agar-gel diffusion in blastomycosis.<sup>32</sup>

Because of the need to demonstrate the organism in order to make the diagnosis of blastomycosis, it is essential that the clinical syndromes suggestive of this disease be recognized. These include the hyperplastic granulomatous, even furuncle-like skin lesions with microabscess formation; combined pulmonary and bone and/or joint destructive inflammatory lesions; and rapidly developing prostatic obstruction associated with a boggy inflamed gland.

## Treatment

Until 1951 there was no effective drug treatment for this disease. Previously many things were used such as iodides, x-ray therapy, and resection, but if active disseminated or pulmonary foci existed, progression was inevitable. In 1951 Schoenbach et al.<sup>43</sup> reported stilbamidine as effective in controlling cases of disseminated blastomycosis. Since that time experience has shown that 2-OH stilbamidine is superior to stilbamidine, but amphotericin B has generally come to be considered the drug of choice.<sup>43, 45, 57</sup> Treatment with either drug is indicated in any patient in whom the diagnosis is made. The danger of late dissemination and progressive disease exists in all infected persons. The only exception may be the reported epidemics of acute pulmonary cases<sup>41, 49, 56</sup> or documented primary pulmonary infection.<sup>1</sup> Similarly single cutaneous lesions without demonstrable pulmonary activity may regress spontaneously or after resection.

At the beginning of treatment extent of the disease should be carefully documented by measuring, counting, and photographing skin lesions; identifying by laminogram the number and character of pulmonary lesions; careful quantifying of other extrapulmonary lesions;

recording of character and severity of systemic symptoms. Treatment should be started with amphotericin B beginning with 1 to 5 mg. and working up to 50 mg. per dose in an adult (1 mg. per kg. in a child but no more than 50 mg.). If the patient is toxic or debilitated by his disease, daily administration is preferred until 150 mg. have been administered, although a blood urea nitrogen value over 50 to 60 may force alternate day administration after the maintenance dose has been reached.

After 1.0 gm. has been given to an adult (20 mg. per kg. to a child), all lesions should be re-evaluated both by physical examination and by culture. If no evidence of activity is present treatment may be discontinued and the patient carefully observed over the next year for signs of reactivation. If the disease is not controlled but has improved steadily, treatment should be continued to an added dose of 0.5 gm. (10 mg. per kg. in a child) and re-evaluation again made. If a total dose of 2.0 gm. (40 mg. per kg. in a child) has been given and the disease is still unstable, or if at any time after the first 0.5 gm. (10 mg. per kg. in a child) of drug has been given the disease is progressive, 2-OH stilbamidine should be started.

2-OH stilbamidine is one of the aromatic diamidines which have activity against *B. dermatitidis* and has proven to be less toxic to man than other diamidines. It is administered intravenously in doses of 225 mg. for an adult. Toxicity includes hepatic dysfunction and fifth cranial nerve neuritis. The total dose administered to an adult is 8.0 gm., which is usually achieved by daily injections of 225 mg. 6 days a week. A period of no administration of drug for up to 2 months follows completion of the 8.0 gm. course. If the disease has not reached clinical control as defined above, a second 8.0 gm. course is then begun.<sup>13</sup>

In some patients 2-OH stilbamidine will be considered for primary treatment because of severe underlying renal disease or other reasons. In these cases the decision to switch to amphotericin B should be based on failure to respond or frank progression of disease after 6.0 gm. of 2-OH stilbamidine have been given. All things considered, including the greater risk of relapse with 2-OH stilbamidine, amphotericin B<sup>13, 35, 57</sup> is the preferred initial treatment of North American blastomycosis.

Hamycin, a drug made in India and tested in the United States briefly showed significant in vitro and clinical effect but more extensive studies have been discontinued for the time being. Toxicity was minimal and the outlook promising.<sup>55, 58</sup>

## CRYPTOCOCCOSIS

### Diagnosis

Infection with *Cryptococcus neoformans* is most dramatically manifested by meningitis, which may be acute and fulminant or indolent with waxing and waning. Almost half the cases are associated with immunosuppression, either iatrogenic or related to disease. Any clinical situation suggesting tuberculous meningitis should include cryptococcal meningitis in the differential diagnosis. Cerebrospinal fluid examination reveals moderate pleocytosis, mainly lymphocytes, moderate elevation of protein, and sugar levels between 15 and 40 mg. per 100 ml. Occasionally signs and symptoms of a space-occupying lesion will be found.

Pulmonary cryptococcosis most often presents as single or multiple nodules with few or no symptoms. X-ray follow-up usually shows little or no progression and calcification is infrequent. Less frequently pneumonic infiltration is seen and the patient is appropriately toxic with cough, sputum and fever. Cavitation may be present, suggesting lung abscess, tuberculosis, or other granulomatous disease.

Extrapulmonary dissemination may be explosive or chronic in nature. Collections of organisms in skin, kidney, or other organs with little or no inflammatory reaction is a bizarre occurrence but is encountered rarely and few if any symptoms are noted.

Culture of *C. neoformans* from spinal fluid, pus, sputum, or other sources usually is easy and should appear in 1 to 10 days. Since actidione inhibits growth of *C. neoformans*, media free of actidione should be used in suspected cryptococcal infection. The colonies are characteristically mucoid but occasionally closely resemble the drier colonies of candida species. Mount of such a culture shows round yeast cells with variable sized capsules. The size of the capsule does not bear on the virulence of the strain encountered.

Direct mount in India ink of spinal fluid or the other sources noted above may show the round, encapsulated yeast cells. This finding is diagnostic in the appropriate clinical situation especially from spinal fluid. It must be mentioned that *C. neoformans* may be seen in sputum when no disease is evident, and the significance of this finding is moot.<sup>61</sup> Again the need to correlate clinical and laboratory findings is evident.

Histologic demonstration of *C. neoformans* in biopsies or resected specimens is made considerably easier using the fungus stains. Differentiation from *B. dermatitidis* may be difficult since both organisms are round and about the same size. If the broad-based bud of blastomyces is not identified then the mucicarmin stain will selectively stain *C. neoformans* and not any other yeast cell. This is a highly useful technique and should be applied while waiting cultural verification.

Serologic demonstration of antibodies by indirect fluorescent or tube agglutination techniques may be deceptively negative in the face of active disease when there is an excess of antigen.<sup>9, 24, 29</sup> The antigen is demonstrable in blood but especially in spinal fluid in active disease even when the organism is not retrieved.<sup>21, 23</sup> The antigen is identified by a latex particle agglutination technique. It seems clear that the demonstration of antigen in spinal fluid with no antibody is indicative of active meningeal involvement. Improvement is suggested by appearance of antibody in serum as titers of antigen fall. Negative antigen testing does not rule out active infection, however.<sup>21</sup>

**TREATMENT.** In all cases in which *C. neoformans* is found to cause a lesion, drug therapy is indicated. Amphotericin B is the drug of choice. 5-Fluorocytosine is a drug which has some in vitro effect on *C. neoformans*<sup>52</sup> and has produced clinical remission in cases of cryptococcal meningitis in which amphotericin was not effective or could not be tolerated.<sup>18, 52, 59</sup> The role of 5-fluorocytosine is not settled because many strains of *C. neoformans* are or quickly become resistant to its effects. Combined or alternating its use with amphotericin may yet prove to be its role. The dose of 5-fluorocytosine is 4.0 gm. per day given for several months.

Cases of meningitis and disseminated cryptococcosis require intravenous amphotericin in daily and then thrice weekly doses as described above.<sup>42, 51</sup> Total intravenous dose is determined by clinical response but 1.5 gm. is considered the minimal effective dose (30 mg. per kg. in children).

Intrathecal therapy is indicated in meningitis when cranial nerve palsy, cerebrospinal fluid block, or depression of consciousness are present. Intrathecal therapy is begun with 0.1 mg. per dose mixed in 3 to 5 ml. of cerebrospinal fluid along with 5 to 10 mg. of hydrocortisone. The dose is increased by small increments to 0.5 to 1.0 mg. given every other day. Total doses of from 5.0 to 30.0 mg. have been reported with successful treatment, the decision being based on clearing of organisms from cerebrospinal fluid as well as clearing of inflammatory cells and other chemical abnormalities. Administration by lumbar puncture is possible but of limited use because of development of arachnoiditis. Cisternal puncture and use of an intraventricular reservoir have also been advocated.<sup>16, 66</sup> Sometimes after amphoteric therapy has been started, cryptococci in large numbers reappear in the spinal fluid, only to disappear subsequently.

Results of intrathecal therapy seem to depend on whether or not underlying immunosuppressive disease exists. If it does, the prognosis is less favorable. This holds true both for control of current active disease and for subsequent recurrence.

When pulmonary cryptococcosis is pneumonic, granulomatous, or cavitary, amphotericin B is clearly indicated and a total dose of 1.5 to 2.0 gm. is usually adequate for cure. When well circumscribed nodules are removed the indication for amphotericin therapy is less compelling.<sup>20, 27</sup> The paper of Campbell, however, makes a strong case for at least 1.0 gm. of amphotericin whenever cryptococcal lesions are found, regardless of their character. The major concern is the late appearance of active extrapulmonary foci such as meningitis.

Treatment of nonmeningeal extra pulmonary cryptococcosis is amphotericin B in a total dose of at least 1.5 to 2.0 gm. The place of 5-fluorocytosine is similar to its use in meningitis, where 4.0 gm. per day should be reserved for those patients who cannot take, or whose organism is unresponsive to, amphotericin. Again, the role of this drug may be as a companion drug to amphotericin.

## COCCIDIODOMYCOSIS

### Diagnosis

Clinical forms of coccidioidomycosis range from acute, generally non-symptomatic, primary infection to a flu-like illness, occasionally with erythema nodosum to progressive coccidioidal granuloma or acute coccidioidal meningitis.<sup>6, 15, 19, 43, 64</sup> Pulmonary disease characterized by cavitation, often thin-walled, may persist when all or almost all symptoms have disappeared. Widespread disseminated coccidioidomycosis may suddenly appear in the course of a debilitating disease such as recurrent pancreatitis, terminal carcinoma, or extensive fibrosis secondary to sili-

cosis. In this syndrome the individual may have resided in the endemic area for many years before persistent viability of the organism can be inferred. Generally, disseminated disease occurs within a few months of geographic exposure.

As implied above the crucial historical fact in diagnosis is residence, albeit brief, in the endemic area of coccidioidomycosis. This includes, generally, the San Joaquin Valley, the San Fernando Valley, and the desert area of California, and the desert areas of Arizona, New Mexico, western Texas, and northwestern Mexico. When such residence is established, the diagnosis of coccidioidomycosis must be considered in any of the clinical situations mentioned above.<sup>6, 19</sup>

Ethnic background is an important consideration in the diagnosis of disseminated infection since persons of Philippine background, Negroes, and Mexican Americans are more susceptible than Caucasians to progressive active disseminated disease.<sup>6, 19</sup>

It is dangerous to culture *C. immitis* in a clinical laboratory, especially when it is only rarely encountered. It is cultured easily from the sputum of cavitory cases and from the lesions of disseminated coccidioidomycosis. A safe procedure is to autoclave the culture and then to make a mount. This will reveal the undisturbed characteristic barrel-shaped arthrospores in chains with intervening protoplasmic sleeves. In primary cases it may be found transiently in sputum or pleural fluid. Biopsy of apparently inactive lesions may yield positive cultures even several years after clinical activity has ceased. Mount of sputum or pus from disseminated lesions or even spinal fluid may reveal the typical spherules which should prompt culture for corroboration. A safer technique than culture is injection of a guinea pig testicle with microscopic study done after 3 to 10 days at which time the spherules will be seen in positive cases.

Biopsy will reveal the spherules with their characteristic endospores. These are easily recognized using the special fungus stains if the proper area in the lesion is chosen. In this disease the demonstration of the organism by either morphology or culture of a biopsy may not always tell whether progressive disease is present. For this the added advantage of the serologic and skin test appraisal of immune mechanisms is invaluable.

Tube precipitin antibodies appear earlier in infection than complement-fixing antibodies. If the immune situation is favorable for the patient, the precipitin test becomes negative early (4 to 6 weeks), but may reappear in case of dissemination. The complement fixation test develops slowly (4 to 6 weeks after infection), reaching its maximum in about 3 months. Rising titer generally implies poor prognosis; falling titer, improvement. Two to 4 weeks after infection the coccidioidin skin test becomes positive.<sup>6, 19</sup>

The exception, in favorable immunologic circumstances, is in isolated cavitory disease where the complement fixation test remains positive and the skin test negative for many months. In all other forms of the infection, this latter set of circumstances indicates the presence of disseminated infection which is not controlled and which must be treated with specific drug. Positive complement-fixing antibodies titers in coccidioidomycosis are often deceptively low, particularly compared with the titers obtained in histoplasmosis.

It is of interest that eosinophilia of 5 to 10 per cent or greater and an elevated sedimentation rate are also signs of active disseminated infection.

It is clear that careful combining of clinical observation with skin test, serology, and mycologic and morphologic examination is necessary for adequate overall understanding of any specific case.

Coin lesions and pulmonary cavities caused by *C. immitis* may be particularly hard to pick up serologically; in cavities, the complement fixation test may be negative in 40 per cent and below 1:16 in the rest.<sup>10</sup> On the other hand, complement-fixing antibodies demonstrated in the spinal fluid are practically diagnostic for meningeal involvement.<sup>28</sup> The colloidal gold curves are helpful in early recognition of meningitis if there is a high first zone.<sup>17</sup>

One problem with the skin test is that in primary infection it may induce an annoying erythema nodosum. For this reason a dilute (1:10,000) solution should be used in that clinical situation.<sup>6</sup> Conversely, the skin test must not be interpreted as negative until a 1:10 dilution is used and is nonreactive in 48 to 72 hours.<sup>6, 19</sup> As in histoplasmosis the skin test is a poor diagnostic tool. Its value is in prognosis of active cases and epidemiology.

## Treatment

Treatment consists of symptomatic measures and, when indicated, amphotericin therapy. Decision as to the use of the drug is based on the clinical syndrome, skin test and serologic data, and the ethnic potential for active dissemination (greatest in Philipinos and Negroes). Self-limited primary infection, regardless of severity of symptoms, requires no drug therapy. Disseminated disease, regardless of other factors, requires drug treatment with total doses sometimes reaching 5 to 10 gm. Meningitis requires intrathecal therapy, apparently at intervals for life, in addition to intravenous administration.<sup>17</sup> This latter may be accomplished by the use of intracisternal injections or an intraventricular reservoir with details of administration similar to those described in the section on cryptococcosis.

Of special interest are those patients with cavitary disease who have sputum positive for *C. immitis*, a significant titer of complement-fixing antibodies, and a possible negative skin test. In spite of the ominous prognostic implication the treatment of choice is resection of the cavity with little or no amphotericin average.<sup>17, 63</sup> This is especially compelling when hemoptysis is present.

Success of treatment has been indicated by clearance of symptoms, disappearance of *C. immitis* from sputum or secretions, development of a positive skin test and fall in titer of complement-fixing antibodies. These variables are often used as indices of how much amphotericin to give in any of the above clinical situations.

A new approach has been to use transfer factor, a preparation of sensitized lymphocytes, to temporarily induce a state of immunologic competence in those patients whose disseminated disease along with a negative coccidioidin skin test and absence of lymphocyte blastogenesis imply

immunologic incompetence.<sup>25</sup> Early results are promising but more experience is necessary to establish the role of this means of treatment. The implications are far reaching indeed.

## SPOROTRICHOSIS

### Diagnosis

*Sporothrix schenckii* has for many years been recognized as a cause of a primary cutaneous ulcerative syndrome which begins with inoculation of the organism from a thorn of a barberry or rose bush, etc. The ulcerations are shallow and resist all but the specific therapy. Spontaneous involution may occur. The lesions follow the distribution of the lymphatics but rarely lead to disseminated disease. Diagnosis is made by culturing the organism from swab or biopsy of the lesions. Pulmonary sporotrichosis has been seen infrequently and is characterized by chronic progressive granulomatous disease which often develops cavities.<sup>2</sup> Rarely, extrapulmonary dissemination is encountered, with meningitis having been the least common manifestation.<sup>62</sup> Diagnosis depends on culturing the organism from the sputum or from aspiration or biopsy of sites within the body.

Skin and serologic tests have not been widely used, although both techniques have been reported experimentally<sup>30, 44</sup> and the complement fixation test is claimed to identify disseminated disease.<sup>30</sup> This is generally unsubstantiated. The specificity of skin test antigens is claimed<sup>11</sup> but awaits general corroboration. Occasional demonstration of the organism in skin and other tissues with special fungus stains and specific immunofluorescence has been useful.<sup>31</sup>

### Treatment

Treatment of the cutaneous form of the disease is orally administered iodides, usually in the form of saturated solution of potassium iodide, 10 to 15 drops in orange juice 3 or 4 times per day. This treatment given for up to two months is almost invariably effective. An amazing example of this was reported in over 2500 cases seen in South Africa.<sup>46</sup>

Pulmonary sporotrichosis is unresponsive to iodides and requires amphotericin B.<sup>38</sup> In the reported experience surgery is often added but whether the lesions would remain controlled without has never been clearly established.

A total dose of amphotericin B of between 1.5 and 2.0 gm. in the adult is the recommended treatment. (In children, 30 to 40 mg. per kg. is recommended.)

It is quite clear that the true incidence of this form of sporotrichosis is unknown since cases are undoubtedly overlooked, because of the difficulty in identifying organisms in tissues and because no reliable screening test is available for accurate epidemiologic testing.<sup>44</sup> Only awareness of the possibility of this infection being the cause of chronic granulomatous disease of the lung will lead to the correct diagnosis whenever it does occur.

## OPPORTUNISTIC INFECTION

In the foregoing discussion only passing mention has been made of the fungal infections encountered in the immunosuppressed host. This has become a highly selective clinical group including patients with diseases such as Hodgkin's disease on one hand and those patients receiving immunosuppressive therapy on the other. The organisms involved may be any of the above, especially *C. neoformans*, but more commonly are species that ordinarily do not produce disease. These include candida and aspergillus species.

Sudden deterioration of such patients with x-ray or clinical evidence of infection warrants immediate search for one of the many other organisms besides the fungi that are opportunists in this circumstance. The use of cultures, biopsies, and serologic tests as noted in the accompanying table will be helpful.<sup>39, 54</sup> Details of this clinical disaster are beyond the scope of this discussion but emergency treatment is indicated.

For candidal infection amphotericin is effective, as to some degree is 5-fluorocytosine.<sup>18, 59</sup> Transfer factor has been used in disseminated cutaneous candidiasis.<sup>36</sup> For aspergillus infection no consistent results have been reported with any agent, although some strains are sensitive to amphotericin B. The most effective approach is reversing the immune state of the host if that is possible.

## SUMMARY

A variety of clinical situations and organisms are grouped under the heading of fungus diseases. Application of clinical skills to recognize syndromes that suggest fungus infection combined with judicious use of cultural, morphologic, and immunologic testing gives the best chance of arriving at a correct diagnosis and initiating proper treatment. In many situations this may be life-saving.

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## Selected Topics in Immunization

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Several comprehensive reviews and compendia of immunizing biologicals currently available or under development have recently appeared in the medical literature.<sup>2, 4, 5, 13, 31, 39, 47, 49</sup> In addition to these useful references the United States Public Health Service and the American Academy of Pediatrics periodically publish revised and updated recommendations on immunization practices.<sup>1, 55</sup> In the discussion which follows, selected topics in immunization will be considered in an attempt to supplement rather than duplicate the material presented in these other publications.

### HAZARDS OF IMMUNIZATION

Despite the spectacular success with which immunizing biologicals have been used in the prophylaxis of infectious diseases, the development of these preparations has not been without cost. Their economic cost is obvious and continues to be an important constraint in the application of immunization programs. Perhaps a more important cost, however, is biological cost—the risk of undesirable reactions to immunization which must be accepted in return for its benefits. An example of this biological trade-off is the production of immunity through deliberate infection of the host with attenuated live viruses such as those contained in vaccines against poliomyelitis, rubeola, rubella, mumps, and yellow fever. Smallpox vaccination is in a similar category because it requires infection of the host with vaccinia virus which results in immunity because of the antigenic similarities between smallpox and vaccinia viruses. In the intact host, infections with these vaccine viruses are mild or inapparent and immunity is produced with little risk to health. In patients whose immune function has been suppressed by drugs or disease, however, these vaccine viruses may cause severe and even fatal infections. This has been experienced with rubeola and smallpox vaccines<sup>18, 36</sup>

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and is theoretically possible with other live virus vaccines. Thus in a category of patients whose need for immunity is great, the immunization procedure carries substantial risk.

Even in the immunologically intact host, vaccine virus infection may be associated with undesirable effects. Rubella vaccines, for example, produce transient arthritis or arthralgia in 1 to 5 per cent of children and in 25 to 40 per cent of women immunized.<sup>29</sup> Complications from smallpox vaccination, in comparison, are very infrequent. In the United States in 1968 complications from smallpox vaccine numbered 75 cases per 1,000,000 primary vaccinations, including avoidable complications such as eczema vaccinatum.<sup>33</sup> The same number of vaccinations resulted in only 3 cases of postvaccinial encephalitis, the most serious complication of this procedure. Nevertheless, the frequency of these complications far exceeds the risk of smallpox exposure in this country and routine immunization against this disease is therefore no longer recommended.<sup>55</sup>

A second risk of immunization is the possibility of reactions to vaccine components. Immunizing antigens must be prepared in some kind of biological system—in embryonated eggs, in tissue cultures of animal or human cells, or in bacteriologic culture medium. All vaccines, therefore, are complex solutions or suspensions which contain many substances with potential biologic activity. When these substances are pyrogenic they produce the fever and malaise associated with vaccines such as those against typhoid, cholera, and influenza. Allergic reactions may occur if the patient is sensitive to antigens such as the egg protein contained in influenza vaccine or to antibiotics which are used to maintain bacterial sterility in tissue cultures used as substrates for the propagation of vaccine viruses. Tests to identify the allergen at fault in the individual patient are complex and usually unavailable or impractical. In the case of a child who developed urticaria and periorbital edema after rubella immunization, for example, dermal sensitivity tests against most of the components of the vaccine were required to show that the patient was allergic to the gelatin stabilizer.<sup>61</sup> Fortunately the risk of these reactions is decreasing because of the development of chemical purification processes such as zonal centrifugation, the use of tissue cultures of avian cells instead of whole embryonated eggs to propagate vaccine viruses, and the use of antibiotics such as neomycin rather than penicillin to maintain the bacterial sterility of the cell cultures.

In addition to triggering already existing hypersensitivity states such as penicillin or egg allergies, sensitization by components of vaccines constitute a third hazard of immunization. It has recently been appreciated, for example, that frequent repeated administration of tetanus toxoid may result in anaphylaxis, or Arthus reaction, or in troublesome urticaria.<sup>11, 40</sup> These reactions are apparently due to the development of skin-sensitizing antibodies against tetanus toxoid. Other clinically important examples of sensitization by vaccines are found in the experience with killed rubeola<sup>17, 37</sup> and respiratory syncytial virus vaccines.<sup>25, 26</sup> In both of these examples, the protective immunity produced by the vaccine declined with passage of time but vaccine-induced sensitivity to these viruses persisted. When natural exposure then resulted in infection, it was often in an atypical and more severe form than in patients who had

never been immunized. Killed rubeola vaccine is therefore no longer recommended and killed respiratory syncytial virus vaccine which was under test when these reactions were noted was never licensed. The emphasis in the development of viral vaccines has since been on the use of live attenuated viruses.

Live virus vaccines raise a fourth problem. They are often prepared in eggs or tissue cultures which may be contaminated with viruses from the species of origin. Many batches of yellow fever vaccine, for example, contained live avian leukosis virus which commonly infects chickens and was therefore present in the embryonated eggs used to propagate the vaccine virus.<sup>21, 33</sup> Special precautions are now taken to maintain leukosis-free flocks as a source of eggs for the production of vaccines. Preparation of vaccines utilizing monkey kidney cell cultures also requires special procedures to detect contamination with any of a variety of simian viruses. After the development of polio vaccine, for example, many early lots were found to contain SV<sub>40</sub> virus, a frequent contaminant of rhesus monkey kidney cell cultures.<sup>32</sup> Both this virus and avian leukosis virus are oncogenic in certain animals and birds.<sup>10, 42</sup> No association between avian leukosis virus and human neoplastic disease has been reported, however, and in a group of recipients of early polio vaccines which were contaminated with SV<sub>40</sub> virus, no deaths from cancer occurred during an 8 year period of surveillance.<sup>15, 16, 35</sup>

Recently a live polio vaccine prepared in cell cultures of human origin has been licensed.<sup>31</sup> Use of human cells to propagate vaccine viruses eliminates any concern about contamination with animal or avian viruses, but raises the question of contamination by human viruses, including human cancer viruses, if such there are.<sup>22</sup> Exhaustive tests have failed to uncover any viruses in these cell cultures of human origin and for all practical purposes they can be considered free of those viruses for which methods of detection are presently available. Continued surveillance of this and all cell cultures used for vaccine production is required, however.

A fifth concern about immunization is related to the role of exogenous antigens as etiologic factors in connective tissue diseases. What is known about the possible cumulative effects of repeated injections of foreign antigens such as vaccines over a patient's lifetime? Intensive immunization of animals has been found to produce amyloidosis, arteritis, and other manifestations of hypersensitivity, but only after administration of antigens in quantities far in excess of those ordinarily used in man. The only comparable study involving humans was done in a group of workers who had undergone intensive immunization because of their employment in biological warfare research.<sup>41</sup> These men received various vaccines and skin test antigens in an average total dose of more than 50 ml. over a period of 8 to 13 years. None of these men experienced clinical illnesses which could be attributed to immunization. During the observation period, 3 men died of coronary occlusion and 1 of carcinoma of the colon. At autopsy no lesions suggestive of immunologically induced disease were detected. Laboratory tests performed on the entire group, however, uncovered several abnormalities which included altered alpha-2 and beta globulins, elevated serum hexosamines, high incidence of

lymphocytosis, increased serum antigammaglobulin activity, and unexplained abnormalities of hepatic and renal function. These abnormalities were not only persistent, but also increased in incidence with continued immunization of this group of men. In the absence of associated clinical illness, the significance of these abnormalities is unknown, but the possibility that they represent early manifestations of incipient disease must be considered.

It is apparent, therefore, that protection by immunization is not achieved without economic and biological costs. Facing every physician is the need to decide whether or not the benefits of immunization justify these costs. Some of the factors involved in the decision to immunize can be expressed in the following equation.

$$\text{Decision to Immunize} \propto \frac{\text{Severity} \times \text{Incidence} \times \text{Efficacy}}{\text{Risk} \times \text{Inconvenience} \times \$ \text{Cost}}$$

The factors in this equation include assessments of the severity of the infection against which protection is sought, its incidence in the patient's environment, and the efficacy of available vaccines to induce protective immunity. Against these considerations the risks, inconvenience, and the monetary cost of the immunization procedure must be measured. Some special circumstances may require inclusion of other variables in the equation, but in general when the numerator in the equation significantly exceeds the denominator, immunization is indicated. When, in contrast, the denominator greatly exceeds the numerator, immunization becomes inadvisable.

Research in the area of vaccine development is presently very active. Type C meningococcal vaccine, for example, has been shown to be effective in the control of meningitis in military populations<sup>2, 3</sup> and vaccines for the prophylaxis of *Haemophilus influenzae* and pneumococcal infections look promising.<sup>2, 43, 47</sup> Many of these new vaccines will probably assume an important place in the prevention of disease, but in deciding on their use in any individual patient, an assessment of the factors in this equation will help weigh benefits against risks.

## BOOSTER DOSES

Among other problems in immunization practice is the question of the need for "boosters." A "booster" is generally defined as a dose of vaccine administered at some interval after primary immunization with the object of stimulating the host's immune response. This response is usually measured in terms of circulating antibody and the "booster" is expected to raise the antibody titer from a low, unprotective level to which it may have declined since primary immunization, to a higher level which will again protect against infection.

With the exception of smallpox vaccination, administration of booster doses is required only for vaccines employing killed microorganisms or their products. The most commonly used vaccines in this group are those against diphtheria, pertussis, and tetanus. The American Aca-

demy of Pediatrics has recommended for many years that a combination of these vaccines be administered as a series of 3 during the first 6 months of life, with booster injections to be given at age 18 months and just before entrance into school.<sup>1, 49</sup>

The need for "boosters" during the school years and in adult life, however, has been a matter of changing opinion over the years. It is generally agreed that the pertussis component of the vaccine should not be given after the age of 4-6 years because the disease is not severe in older children and adults, its incidence is low, and the risk of vaccine reactions increases with repeated use. Diphtheria, however, continues to be a serious disease throughout life and although reactions to diphtheria toxoid also increase with repeated use, booster injections at 10 year intervals after age 4 to 6 are recommended.<sup>1, 49</sup> To reduce sensitivity reactions to diphtheria toxoid, its concentration in vaccines for adult use is only 15 to 20 per cent of that in the DPT vaccine used for immunization of infants and preschool children.

Like diphtheria, tetanus is a serious disease at any age and because the organism is ubiquitous it is important to maintain life-long immunity against it. Fortunately tetanus vaccine is one of the most effective immunizing agents available and once primary immunization (i.e., 3 doses of tetanus toxoid) is achieved, protection can be maintained by booster doses given at 10 year intervals. In connection with severe trauma an emergency "booster" is recommended if none has been given in the previous 5 years because of the possibility of intense exposure in the presence of necrotic tissue which may occur in this situation.<sup>55</sup> More frequent use of tetanus toxoid is contraindicated because it serves no purpose and increases the risk of vaccine reactions.<sup>11, 40</sup> Tetanus toxoid combined with the appropriate adult dose of diphtheria toxoid is available as a preparation referred to as Td. This can be given as a booster dose every 10 years, or in a series of 3 injections (second dose 4 to 6 weeks after the first, third dose 6 to 12 months after the second) for primary immunization of those persons who were not immunized in infancy or early childhood.<sup>55</sup>

Another killed preparation requiring periodic "boosters" is influenza virus vaccine. Unlike tetanus toxoid, killed influenza viruses are poor antigens and boosters must be given yearly to maintain immunity. Because of this inconvenience and the febrile reactions which sometime follow administration of the vaccine, its use is recommended only in persons with chronic debilitating illnesses, especially those of cardiopulmonary origin. Influenza vaccine viruses are prepared in embryonated eggs and should not be administered to persons who are hypersensitive to egg protein.<sup>56</sup>

With live virus vaccines, booster doses in the years following primary immunization are generally considered unnecessary. The antibody titers induced by live virus vaccines, such as that for rubeola, decline with passage of time, as do titers induced by natural infection.<sup>29</sup> In both situations, however, the residual titers are adequate for protection.

In the case of trivalent live oral polio vaccine, it is recommended that in addition to the 3 doses required for primary immunization in infancy, repeat doses of vaccine be given at ages 18 months and 4 to 6 years.<sup>1, 49</sup> It

is also recommended that previously immunized travelers planning to enter an endemic area receive an additional dose of polio vaccine.<sup>55, 58</sup> These doses, however, are not given for the purpose of raising antibody titers. Trivalent polio vaccine contains the attenuated strains of the 3 types of polio viruses, and a single oral dose of the vaccine seldom results in infection by and antibody response to all 3 types. Repeat doses are therefore administered on the premise, which is a sound one, that a type which does not infect on the first or second dose will do so on the third, fourth, or fifth dose. In addition the original polio vaccines were monovalent, and therefore a person immunized in the early 1960's might have failed to receive all 3 polio virus types or perhaps inadvertently received the same type twice. If such doubts exist with respect to a patient's protection, the situation can be remedied by giving a dose of trivalent vaccine to induce infection with and antibody response to whatever type was missed earlier.

With regard to rubeola, rubella, and mumps, only one strain of virus is responsible for each disease and infection and immunization result from one injection of each of these vaccine viruses. In patients whose initial immunization to rubeola was with killed rubeola vaccine, re-immunization with live attenuated rubeola vaccine is recommended. Again, this is not a booster dose, but constitutes immunization with a different and much more effective vaccine. Re-immunization is also recommended for patients whose initial dose of attenuated rubeola vaccine was given before 1 year of age.<sup>55</sup> Transplacentally acquired maternal antibody against rubeola virus commonly interferes with the infant's antibody response, and re-vaccination at a later time is necessary, not as a booster dose, but because the patient was originally immunized under circumstances in which he could not respond optimally.

Since live attenuated virus vaccines have been in use for less than 15 years, it remains to be seen whether or not the immunity they induce will last through a lifetime. At present, however, the evidence is that immunity induced by live virus vaccines follows the pattern of immunity acquired by natural infection.

## IMMUNIZATION DURING PREGNANCY

In general it can be said that the time for concern about immunity in the pregnant woman is before pregnancy occurs. With vaccines, as with other medications, it is prudent to give as few as possible during pregnancy. If the need for immunization arises during pregnancy, only a few guidelines are available because studies of the effects of immunization on pregnant women cannot be justified, except those done in retrospect or in women who have elected to undergo abortion.

Vaccines incorporating killed organisms or their products have no infectious potential, and therefore could be given during pregnancy without risk of infecting the fetus. Vaccine reactions of the types previously discussed can occur, but none of these reactions has been found to be specifically harmful during pregnancy.

With live virus vaccines, however, the risk of infection of the fetus is

very real. In natural infections, transplacental transmission has been documented for many viruses and it can be assumed that some vaccine viruses will also cross the placenta. Rubella vaccine, for example, has been given inadvertently during pregnancy and in planned studies to pregnant women about to undergo elective abortion. The results of these studies showed that the fetus can be infected by rubella vaccine virus.<sup>34, 59</sup> Although the teratogenic potential of rubella vaccine virus has not been established,<sup>57</sup> it should not be administered during pregnancy.

Oral poliovirus vaccine has been given to large numbers of pregnant women without detrimental effect and is not regarded as contraindicated in pregnancy if protection is required.<sup>50, 55</sup> Nevertheless, in view of the knowledge that several viruses can have marked deleterious effects on the fetus, the administration of live virus vaccines during pregnancy seems generally unwise.

### RABIES PROPHYLAXIS

An infectious disease which occurs in the United States with a frequency in man of 2 cases a year, but against which over 30,000 persons a year receive emergency immunization, is rabies. On a worldwide basis there were 515 deaths from rabies in 1968 and 674,000 persons were vaccinated.<sup>41</sup> Rabies immunization is therefore a procedure of considerable importance.

After possible exposure, usually from an animal bite, the decision of whether or not to immunize is a difficult one because the disease is rare and the immunization procedure is long and unpleasant. Two killed virus vaccines have been used, one prepared in embryonated duck eggs and the other in rabbit brain. The efficacy of the two vaccines is approximately equal,<sup>55</sup> but because of the rarity of human rabies and the ethical considerations involved in conducting controlled comparisons in man, there are not much data on which to base this conclusion.<sup>9, 42</sup> Local reactions often occur at the sites of injection of both vaccines, but more importantly, nervous tissue vaccine can cause neuromuscular complications. Since duck embryo vaccine rarely causes serious reactions,<sup>46</sup> it is the preferred preparation and is the only human rabies vaccine commercially available in the United States at present. For patients who are allergic to avian products, and in whom a significant possibility of rabies exposure has been documented, a rabies vaccine prepared in cultures of hamster kidney cells is available through consultation with the United States Public Health Service, Center for Disease Control, Atlanta, Georgia.

For passive immunization, an anti-rabies serum of equine origin can be obtained commercially, and in combination with vaccine constitutes the most effective post-exposure prophylaxis available.<sup>55</sup> Because of the equine origin of this serum, patients must be tested for hypersensitivity of the immediate type before it is administered. Patients who will develop manifestations of delayed hypersensitivity to horse serum cannot be identified by these tests, however, and serum sickness reactions can be expected to occur in approximately 20 per cent of recipients. When treatment with antiserum is required in a patient who is known to be

allergic to horse serum, an anti-rabies immune serum globulin of human origin can be made available through consultation with the Center for Disease Control.

Most often the bite which causes concern about rabies is inflicted by a dog and the extent of post-exposure therapy required may vary from no treatment in the case of a bite by a healthy dog which is being kept under a veterinarian's surveillance, to administration of antiserum in conjunction with 21 doses of vaccine when the animal is rabid or suspected of being rabid. The approach to each patient must be individualized but a few useful generalizations can be made. Since wildlife are the main reservoir for rabies, all except clearly provoked bites by wild carnivorous animals, usually skunks, foxes, and raccoons, or by bats should be considered as a rabies exposure, and both vaccine and antiserum should be given. Although any warm blooded animal may contract rabies, bites by squirrels, chipmunks, rats, and mice almost never warrant rabies prophylaxis because of the rarity of the disease in these species.<sup>55</sup>

Inquiring about the circumstances of the bite may also be helpful. An unprovoked bite, because it represents unusual animal behavior, is cause for more concern that an animal might be rabid than a bite which is associated with trapping wildlife or a child's tantalizing a dog, since in both situations even a healthy animal might be expected to bite. Knowledge of whether the biting animal has received rabies vaccine is also very helpful, since rabies is unlikely to occur in an immunized animal.

Decisions at the extremes of circumstances are easy. A provoked bite by a healthy, immunized dog which is under a veterinarian's observation requires no anti-rabies prophylaxis. An unprovoked bite by an unknown dog which escaped, or any unprovoked bite by a skunk, fox, raccoon, or bat clearly requires administration of both vaccine and antiserum. Situations in between are much more difficult. Some help can be obtained from the widely published World Health Organization guidelines<sup>40, 55</sup> and from a useful review of the problem of rabies prophylaxis by Plotkin.<sup>42</sup> Ultimately, however, it is left to the individual physician to compare the risks and benefits of instituting or deferring prophylaxis in the specific situation with which he is confronted and then to make the decision on whether or not to immunize.

## IMMUNIZATION FOR INTERNATIONAL TRAVEL

Because of the increasing ease and availability of long distance transportation, physicians are frequently consulted about immunization for international travel. The immunization requirements for various countries are detailed in a very useful government publication entitled, "Vaccination Certificate Requirements for International Travel."<sup>58</sup> In addition to listing the vaccinations required for travel to various foreign countries, this booklet also contains the recommendations of the United States Public Health Service about other immunizations advisable for the traveler's protection. For direct travel between the United States and Europe there are no immunization requirements, except that if a smallpox or cholera outbreak occurs in a country visited by a traveler, most countries

remaining on his itinerary will require smallpox and cholera certificates. Such outbreaks are unlikely in Europe but travelers whose itineraries are long and complicated, or to whom delays are unacceptable, might consider these immunizations.

The cholera vaccine presently available is regarded by the United States Public Health Service as only 50 per cent effective in preventing symptomatic infection and of no value in preventing transmission of infection.<sup>55</sup> Two injections are required for optimal effect but, curiously enough, a vaccination certificate requires only one. Reactions are much like those to typhoid vaccine, with local discomfort sometimes accompanied by fever and malaise.

Travelers to areas in which yellow fever is endemic must be vaccinated against this disease. For the purpose of an international certificate the patient must go to a certified vaccination center usually operated by the United States Public Health Service. This is because yellow fever vaccine, a live virus preparation, is extremely sensitive to heat and therefore must be stored frozen, reconstituted with diluent before use, and used within 60 minutes of reconstitution. Unsupervised use of this vaccine might result in administration of an inactivated and immunologically ineffective product.

For travel to Asia, Africa, and many countries of South America, typhoid vaccine is recommended, as is immune serum globulin for prophylaxis against hepatitis. It is also most important to make certain that travelers have at some time completed primary immunization with trivalent oral polio vaccine, and for those who plan to visit areas with primitive sanitation, a repeat dose of vaccine is recommended to ensure immunity against all 3 types of poliovirus.

## SMALLPOX VACCINATION

Smallpox vaccination for international travel raises the general issue of the need for immunization against this disease. Routine immunization against smallpox is now felt to be inadvisable in the United States because the risk of complications from the procedure, although low, exceeds the risk of exposure to the disease.<sup>1, 55</sup> Even when preventable complications such as eczema vaccinatum are excluded, the risk of unpredictable serious reactions such as postvaccinial encephalitis is greater than that of contracting the disease.<sup>32</sup> The continued control of smallpox in this country will now be based upon rapid detection and isolation of imported cases and immediate vaccination of the potentially exposed population. Because the frequency of postvaccinial encephalitis following primary vaccination has been shown to increase with age after the first year of life,<sup>6, 33</sup> the concern has been raised that primary immunization of large numbers of adults in such an emergency situation might inflict this complication on persons in whom it would have been avoided by immunization at an earlier age. Other groups who, if unimmunized in childhood, may face primary vaccination in adult life are medical personnel, military recruits, and travelers to countries where smallpox remains endemic.

Although the risk of postvaccinial encephalitis might be increased in these situations, the very high rates sometimes cited for this complication in adults usually refer to the European experience especially in Dutch military recruits and may have been related to peculiarities of the strain of vaccine virus used in that population.<sup>48, 60</sup> These high rates have not been encountered in military recruits in the United States.<sup>32</sup> Despite the fact that postponement of primary vaccination until adult life may increase the risk of postvaccinial encephalitis in certain groups, it is estimated that the overall risk of postvaccinal complications will be lower than if the policy of routine smallpox immunization in early childhood were continued.

Another point of view which has been raised is that a better course of action would be to develop an effective but less hazardous vaccine rather than to abandon routine smallpox vaccination. An attenuated strain of vaccinia virus has been developed for use in patients with eczema, for example. The frequency of complications from the standard vaccine is so low, however, that administration of many millions of doses of any new vaccine would probably be required to demonstrate a statistically significant reduction in the rate of postvaccinal complications.

The worldwide campaign to eradicate smallpox has resulted in a marked decline in the incidence of this disease in recent years.<sup>42</sup> It is not an unrealistic hope that the success of this program may eventually obviate the need for smallpox immunization despite the increasing ease with which a traveler and the microorganisms he harbors can reach any part of the world.

## HUMAN IMMUNE SERUM GLOBULIN

Pooled human immune serum globulin contains IgG in a concentration which is about 25 times that of normal blood. Although it probably contains antibodies against a variety of infectious agents, it is effective in the prophylaxis of only a few infections. Susceptible patients exposed to rubeola and anyone exposed to infectious hepatitis (hepatitis A) should be given pooled immune serum globulin promptly after exposure because it has been shown to effectively prevent or ameliorate these diseases.<sup>1, 28, 50, 51</sup> In addition it should be administered to persons who anticipate frequent, prolonged, or intense exposure to infectious hepatitis.<sup>55</sup> There is also evidence that it modifies the course of varicella if given promptly after exposure.<sup>44</sup> It should be considered, therefore, in exposed susceptible patients at special risk from this infection, such as those whose immune responses have been depressed by drugs or disease. Pooled immune serum globulin is also effective as replacement therapy in hypogammaglobulinemic states.<sup>24</sup> In persons exposed to rubella, however, its effect is extremely variable. The rubella exanthem is often prevented by administration of immune serum globulin after exposure,<sup>19, 30</sup> but other aspects of the infection, including viremia, often progress as in the unaltered disease.<sup>50</sup> In the pregnant patient, therefore, protection of the fetus against blood borne transplacental infection is not assured.

There is little evidence to suggest that pooled immune serum globulin is of any value in the prevention or modification of other infections including mumps, serum hepatitis (hepatitis B), herpes simplex virus infections, and respiratory infections. Specific human immune serum globulin has been shown to be of value in the prevention of tetanus<sup>15</sup> and varicella-zoster infections,<sup>7, 8</sup> and in the treatment of vaccinia virus infections.<sup>31</sup> Tetanus immune globulin is commercially available. Varicella-zoster and vaccinia immune globulins, however, are in very short supply and must be obtained, when available, through the consultants listed in references 1 and 55.

Although complications from the administration of immune serum globulin are rare, hypersensitivity reactions such as anaphylaxis occasionally occur, especially after inadvertent intravenous injection. These reactions may be related to the antibodies against IgG which develop in many recipients after repeated doses of immune serum globulin or other blood products containing immunoglobulins.<sup>5, 12, 27, 48</sup> Although these observations should never preclude the administration of immune serum globulin in situations in which its value has been demonstrated, the indiscriminate use of this product cannot be regarded as inconsequential and should be curtailed.

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## New Antituberculosis Drugs and Concepts of Prophylaxis

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### NEW ANTITUBERCULOSIS DRUG REGIMENS

In recent years, several major changes have taken place in the chemotherapy of tuberculosis. New drugs have been introduced and better means of utilizing the available drugs have been established.

#### Realignment of Drugs

The antituberculosis drugs traditionally have been divided into "first line," "second line," and "reserve" categories. Formerly, the first line group consisted of isoniazid, para-aminosalicylic acid (PAS), and streptomycin. PAS has always been a disagreeable drug to take, and the gastrointestinal side effects made it difficult for many patients to tolerate it. In addition, febrile and allergic reactions to PAS were not uncommon. Ethambutol produces relatively few unpleasant side effects, and the one important toxic effect, optic neuritis, is very rarely seen at the presently recommended dosage of 15 mg. per kg. of body weight per day.<sup>12</sup> Rifampin<sup>3</sup> is a semisynthetic antibiotic which is very active against *Mycobacterium tuberculosis* and some of the "atypical" mycobacteria. It has been used mainly in combination with isoniazid, ethambutol, or both. When given daily its toxicity is low, on the same order as that of isoniazid. Approximately 4 per cent of patients treated with rifampin daily have manifested transient chemical abnormalities of hepatic function and approximately 1 per cent have exhibited clinical hepatitis. The incidence of overt hepatitis varies widely in different reported series and seems to be more common in patients who are treated with the combination of isoniazid and rifampin.

The first line drugs, those used most commonly for initial treatment, now consist of isoniazid, rifampin, ethambutol, and streptomycin. Those used for re-treatment, or whenever the above are not suitable, are ethionamide, cycloserine, pyrazinamide, and PAS for oral administration; capreomycin, viomycin, and kanamycin for parenteral use.

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## Drug Regimens

There has been controversy for many years about the relative efficacy of two-drug as opposed to three-drug regimens for the treatment of active tuberculosis. Now that three first-line drugs are available which can be given orally, there should be less objection to using a three-drug regimen for initial treatment. Our recommendations for the routine initial treatment of tuberculosis in adults are as follows: For minimal or early moderately advanced disease without complications, isoniazid and ethambutol should be given for 2 years. For far advanced pulmonary, for extrapulmonary, or for disseminated disease, isoniazid, ethambutol, and rifampin should be administered for 3 to 6 months depending upon extent of disease and response to treatment, followed by isoniazid and ethambutol for the remainder of 2 years and possibly isoniazid alone for a third year. There are some who recommend treatment with isoniazid and rifampin for all but minimal cases because of the more rapid conversion of sputum cultures from positive to negative for mycobacteria. This consideration may be valid if the slightly faster conversion rate is confirmed by further large-scale studies.

## Single Versus Divided Doses

It is now clear that all the oral antituberculosis drugs may be given in a single daily dose rather than in divided doses without sacrificing any therapeutic effect. Cycloserine, ethionamide, and PAS, however, should be administered in two or three divided doses daily to diminish toxic reactions and unpleasant gastrointestinal side effects. The greater convenience of the once-a-day regimen without increase of undesirable reactions makes this the method of choice for administration of all but these three. Rifampin should be taken when the stomach is empty for maximum absorption.

## Treatment of Children

Most of the recent authoritative recommendations for the treatment of tuberculosis in children retain the old drug regimens:<sup>25</sup> For uncomplicated and asymptomatic primary disease, isoniazid alone or isoniazid plus PAS for 1 to 2 years; for complicated, extrapulmonary, or disseminated disease, triple therapy consisting of isoniazid, PAS, and streptomycin, with the streptomycin being discontinued after the disease appears to be well under control and a total duration of at least 2 years. Substitution of ethambutol and rifampin as companion drugs for isoniazid would be desirable to obviate the undesirable side effects of the administration of PAS and the necessity for daily injections of streptomycin. Unfortunately, data on the administration of these drugs to children are scanty and the package brochures advise against their use. In reports involving approximately 100 children in France, Brazil, and Romania,<sup>7, 10, 20, 30</sup> there were no adverse effects from the use of ethambutol. In approximately 200 children given rifampin there were 24 instances of chemical dysfunction of the liver and 5 cases of clinical hepatitis with jaundice, apparently all in children receiving the combination of isoniazid with rifampin.

For the initial therapy of overt primary tuberculosis in children we recommend the use of two drugs for one year, to be followed by administration of isoniazid alone for another year if the disease is extensive. Until further experience is gained with the new drugs, isoniazid and PAS should be started in children too young to test for visual acuity. Ethambutol may be substituted if PAS is not tolerated. The combination of isoniazid and ethambutol may be used to initiate treatment in older children. In the presence of disseminated disease, especially meningitis, a third drug should be given; rifampin is superior to streptomycin in this regard because of its better penetration into the cerebrospinal fluid.<sup>11</sup>

The problem of the use of second line drugs for the treatment of drug-resistant tuberculosis in children has been reviewed by Steiner.<sup>31</sup> Cycloserine appears in the spinal fluid in good concentrations and its use has not been associated with adverse effects in the small number of children included in published reports.<sup>29</sup> Ethionamide has been given to children intravenously and by rectal suppositories as well as by the oral route with less toxicity than that seen in adults.<sup>17, 19, 21</sup> It too, penetrates well into the spinal fluid.

### Supervised Intermittent Drug Treatment

One of the most difficult problems in the successful treatment of tuberculosis has been the large proportion of patients who do not take their drugs regularly for the required length of time. Recently, a possible solution to this problem became available when it was demonstrated that after a preliminary period of approximately 3 months of daily treatment, supervised drug therapy could be continued on a twice weekly basis without sacrificing therapeutic efficacy.<sup>16, 23</sup> The intermittent regimen of proven value consists of isoniazid, 15 mg. per kg. orally (with pyridoxine 50 mg.) and streptomycin 20-25 mg. per kg. intramuscularly, each given by a nurse or other suitably trained individual at a convenient location on a twice weekly basis. Approximately 10 per cent of patients may be expected to show adverse side effects, mainly from the streptomycin injections. The combination of isoniazid and PAS orally twice weekly was found to be successful in one trial, but there was a slightly higher proportion of failures with isoniazid-resistant organisms as compared with a daily drug regimen, and the efficacy of the twice weekly regimen, unlike the daily, was influenced by the extent of disease and the sputum bacillary count.<sup>32</sup> The combination of twice-weekly isoniazid with ethambutol, 50 mg. per kg., is being investigated and the preliminary reports are favorable.

Rifampin is theoretically suitable for intermittent treatment but serious allergic and hematologic reactions have been reported when the drug is given once or twice a week.<sup>5, 27</sup> These may be divided into the following categories: Cutaneous (flushing, itching, and hives), abdominal (pain, nausea, and vomiting), influenza-like (fever and aching), respiratory (anaphylactoid or asthmatic), and hematologic (anemia, thrombocytopenia, and purpura). The first four varieties usually occur 2 to 3 hours after a dose of rifampin and are gone within 12 hours. In one study,<sup>5</sup> the rate of reactions with a dose of 1200 to 1800 mg. per dose was 56 per cent on a once weekly schedule. When the dose of rifampin was decreased to

900 to 1200 mg., the rate was 42 per cent on a once weekly schedule and 17 per cent on a twice weekly schedule. In another study it was necessary to discontinue the regimen in 22 per cent of patients who were given 1200 mg. of rifampin twice weekly.<sup>27</sup> These reactions were considered to have an immunologic basis since rifampin-dependent antibodies were found in the serum of involved patients. Similar hypersensitivity reactions occur very infrequently when rifampin is given on a daily basis.

## CONCEPTS OF PROPHYLAXIS

Preventive treatment for the control of tuberculosis has gained wide acceptance since the cooperative studies of the United States Public Health Service began in 1955.<sup>15</sup> The requirements for a satisfactory prophylactic antituberculosis drug are effectiveness when taken by mouth once a day, lack of significant toxicity and adverse side effects, and low cost. Isoniazid appears to satisfy these requirements. The concept of preventive treatment with isoniazid was first tested in guinea pigs.<sup>6</sup> The animals were pretreated for 2 weeks with isoniazid in the drinking water and then were challenged with virulent tubercle bacilli. It was found that the degree of protection from infection depended upon the number of bacilli injected, the dose of isoniazid, and the duration of drug treatment following infection.

Extensive reviews<sup>14</sup> and authoritative statements on isoniazid prophylaxis are plentiful. In this presentation, we will emphasize only a few special considerations.

### Toxicity of Isoniazid

As with any other drug, the possible benefits to be derived from isoniazid treatment must be weighed against the risk of prolonged administration of the agent. Allergic manifestations such as fever and rash occur infrequently. That arthritis and the lupus syndrome may be associated with the administration of isoniazid has been known for some time.<sup>2</sup> Indeed, studies have shown that a positive blood test for antinuclear factor may be found in 20 to 80 per cent of patients on long-term treatment. The significance of this finding remains to be determined and requires prolonged follow-up observations.

### Case Report

A 58 year old hospital employee was admitted to Cleveland Metropolitan General Hospital on January 14, 1971, after the acute onset of chills, spiking fever, generalized myalgias, and arthralgias. A preliminary diagnosis of "flu syndrome" was made. Isoniazid prophylaxis had been started 10 days previously because his PPD skin reaction, previously negative, was found to be positive on routine testing. The symptoms abated promptly without treatment and isoniazid was not resumed. The patient's serum was strongly positive for antinuclear factor. It was still positive 2 years later although the patient was healthy and asymptomatic.

Hepatitis is the most important and the most disturbing of the reactions to isoniazid. Generally considered to occur in approximately one in 1,000 patients, an alarming high rate of hepatitis has been reported recently in patients receiving isoniazid prophylaxis. In a study from

Washington, D.C., the incidence was 1 per cent and there were 2 deaths.<sup>18</sup> In a series from Baltimore, there were 7 deaths among 3000 patients (communication from United States Public Health Service). The problem is compounded by the difficulty in distinguishing isoniazid toxicity from viral hepatitis and by the fact that enzyme elevations during the early weeks of isoniazid administration can be documented in approximately 10 per cent of patients. These elevations are usually transient but evidence of hepatocellular damage has been confirmed by liver biopsy in some asymptomatic patients.<sup>25</sup> A recent report from Johns Hopkins Hospital in Baltimore documents 14 instances of isoniazid hepatitis including 3 deaths in persons taking isoniazid for prophylaxis.<sup>26</sup> These reports along with other published data suggest that the rate of clinical hepatitis apparently is close to 1 per cent. In a group of 427 hospital employees receiving isoniazid for prophylaxis, 3 per cent showed either clinical hepatitis or elevations of bilirubin or alkaline phosphatase or both, for which the drug had to be discontinued.<sup>6</sup> At this time, it is not clear whether patients on isoniazid prophylaxis should be followed by repeated liver function tests or by careful questioning about symptoms at monthly intervals and warnings to report such symptoms promptly. It has been recommended that the drug be given only on 5 consecutive days of each week to reduce the risk of hepatitis, but no controlled studies on the efficacy and relative safety of this regimen have been reported as yet.

### **Initiation of Prophylaxis is Only the Beginning**

The physician must make an effort to assure that the prophylactic drug will be taken regularly for the prescribed length of time. Studies have shown that only 60 to 75 per cent of patients take their medication properly. It is useless to prescribe preventive treatment without making adequate provision for regular follow-up and supervision, especially with children.

### **Isoniazid-Resistant Bacilli**

Obviously, it would be unwise to attempt preventive treatment with isoniazid if the disease of the patient or of the index case was caused by isoniazid-resistant bacilli. A careful history should be taken to exclude exposure to known drug resistant organisms. It is the duty of the physician to check the drug sensitivity of the tubercle bacilli from the index case. Is there a substitute drug for prophylaxis? Rifampin would be a logical candidate except that it is quite expensive and there is no proof yet that it is effective for this purpose.

### **Emergence of Drug Resistance During Preventive Treatment**

One instance of possible emergence of resistance to isoniazid during prophylactic therapy was reported from this hospital.<sup>21</sup> Additional published information is very scanty but Ferebee in 1967 provided information on 44 patients to whom isoniazid had been given for "inactive" disease; isoniazid-resistant organisms were isolated later from 20 per cent of these patients as compared with 5 per cent of 108 controls who had received placebo.<sup>13</sup> Evidently this will not be a major problem provided that patients who apparently have inactive disease are studied ade-

quately before treatment and those who have positive sputum cultures are treated for *active* disease.

### **Not All Positive Tuberculin Tests in Children Are Due to Infection With *Mycobacterium Tuberculosis***

The possibility of infection with *Mycobacterium marinum* acquired from swimming pools or aquariums, and lymphadenitis due to *M. scrofulaceum*, should be considered in children who have positive tine or intermediate strength PPD tests, especially in those who show weak or doubtful reactions. At least the proper questions should be asked and the child should be examined for the presence of lymph nodes and scars in the neck before giving prophylaxis.

### **Does Isoniazid Eliminate Dormant Tubercle Bacilli?**

The major purpose of preventive treatment for patients with inactive tuberculosis or recent infection is to reduce the chance of development of overt disease within the next few years. There is adequate documentation that it accomplishes this purpose.<sup>11</sup> It is also given in the hope of reducing the *late* reactivations but it should be remembered that isoniazid is bactericidal only for actively multiplying bacilli; in vitro experiments indicate that resting cells are not damaged by the drug<sup>22</sup> and therefore it cannot be expected to sterilize lesions containing dormant bacilli. It has been shown that preventive treatment reduces the rates of active disease by 60 to 80 per cent (not 100 per cent) during the year of treatment and that it has some benefit for the succeeding 6 years,<sup>14</sup> but the long-term effect on late reactivations is not yet known. If a reduction of the reactivation rate is still evident after 15 to 20 years our concepts of the mechanism of action of isoniazid and latency of bacilli in inactive lesions will need to be revised.

### **Active Tuberculosis Following Prophylaxis**

Two recent case reports of active tuberculosis developing several years after preventive treatment had been given could represent instances of either exogenous reinfection or exacerbation of disease caused by latent bacilli which had not been eliminated by isoniazid.<sup>1, 3</sup> Active tuberculous disease following prophylaxis in silicotics also has been reported.<sup>4</sup>

In summary, some of the indications for preventive treatment are well established and should not be changed despite the increased evidence for the reality of isoniazid hepatitis. Those who should receive isoniazid prophylaxis include household contacts of infectious cases, recent converters of any age, positive tuberculin reactors under the age of 18 to 20 years, and positive reactors at special risk, such as those immunosuppressed by disease or drugs. For adults who have inactive disease and those who have recovered from tuberculosis without having had adequate chemotherapy, would it not be better to regard isoniazid prophylaxis as an investigation which is still in progress rather than as a treatment of established value? Such patients should be studied intensively to identify those who have smoldering active disease who should

be treated as cases of active tuberculosis. As for the treatment of all positive tuberculin reactors regardless of age, the risk of isoniazid toxicity in this group of adults would appear to be greater than the risk of active disease. Several of the adult patients reported by Maddrey and Boitnott who developed clinical hepatitis, including two who died, were apparently given preventive treatment solely on the basis of a single positive tuberculin skin test.<sup>26</sup>

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